VOL. 14 • NO. 11 • NOVEMBER 2019

CHEST® Physician

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Guidelines updated for treating community-acquired pneumonia

BY MARK S. LESNEY
MDedge News

An update to the 2007 guidelines on the treatment of community-acquired pneumonia (CAP) was published by two medical societies, based upon the work of a multidisciplinary panel that "conducted pragmatic systematic reviews of the relevant research and applied Grading of Recommendations, Assessment, Development, and Evaluation methodology for clinical recommendations."

The panel addressed 16 questions in the areas including diagnostic testing, determination of site of care, selection of initial empiric antibiotic therapy, and subsequent management decisions. Some of their recommendations remained unchanged from the 2007 guidelines, but others were updated based upon more-recent clinical trials and epidemiological studies, according to Joshua P. Metlay, MD, of Massachusetts General and colleagues on behalf of the Infectious Diseases Society of America and the American Thoracic Society.

Among the key recommendations differing from the previous guidelines, the 2019 guidelines include the following:

- Sputum and blood culture samples are recommended in patients with severe disease, as well as in all inpatients empirically treated for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*.

GUIDELINES // *continued on page 6*

CDC, FDA in hot pursuit of vaping lung injuries' source

BY THERESE BORDEN
MDedge News

The national outbreak of vaping-associated lung injuries is ongoing, and the number of cases and deaths continues to rise.

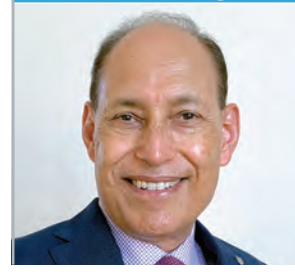
The Centers for Disease Control and Prevention is providing frequent updates of the wide-ranging and aggressive investigation of the cases and deaths linked to vaping, and although a definitive cause remains unknown, evidence is accumulating to implicate tetrahydrocannabinol (THC)-containing devices.

The investigation is being conducted in concert with the Food and Drug Administration, state and local health departments, and public health and clinical partners.

The acronym EVALI has been developed by CDC to refer to e-cigarette, or vaping products use–associated lung injury. In a report summarizing data up to Oct. 31, CDC reported 1,888 EVALI cases and 37 deaths. These cases have occurred in all U.S. states (except Alaska), the District of Columbia, and the U.S. Virgin Islands. The CDC also published a report in the Morbidity

VAPING // *continued on page 7*

INSIDE HIGHLIGHT



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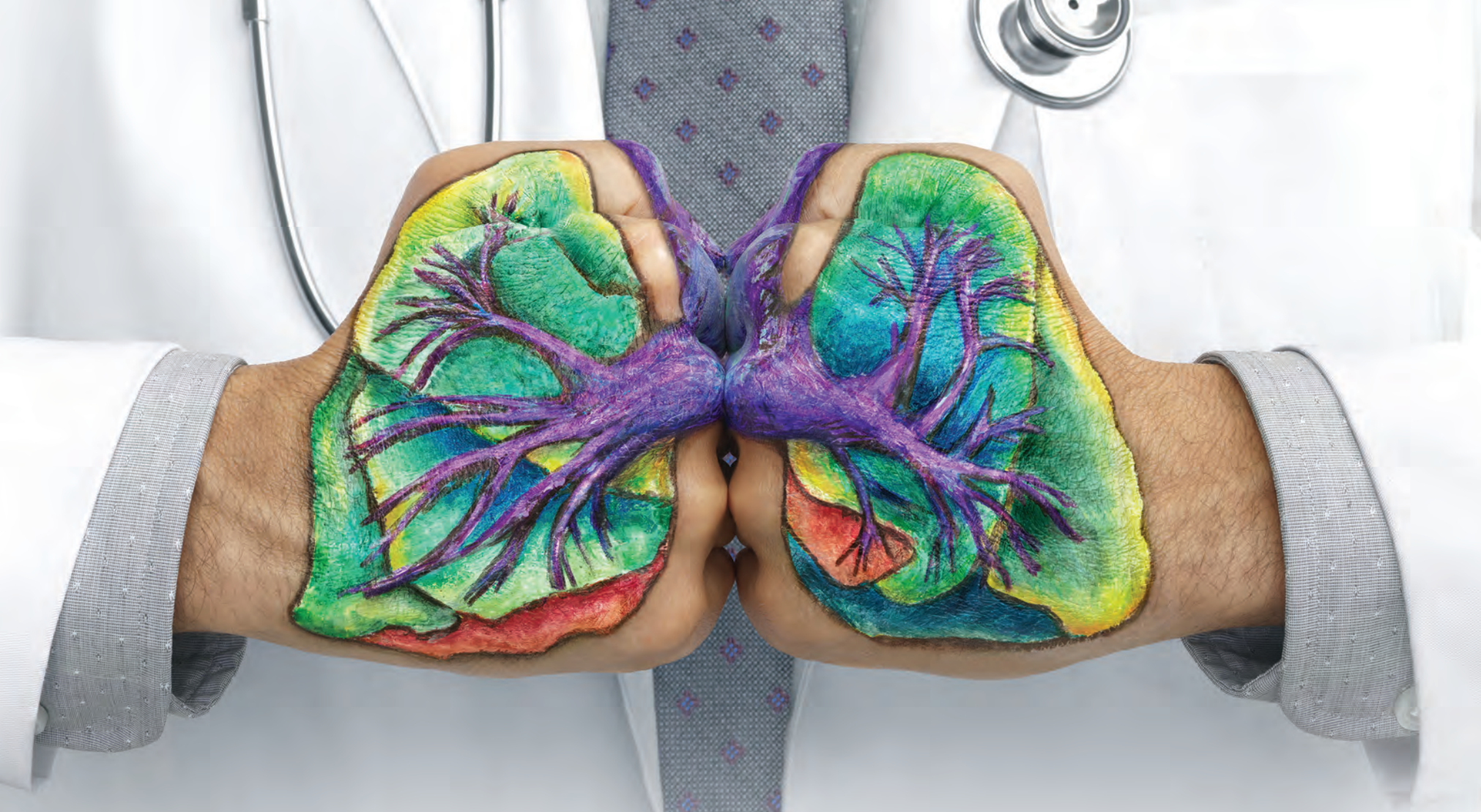

Indication

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

Elevated liver enzymes and drug-induced liver injury (DILI): DILI has been observed with Esbriet. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3x ULN (3.7%) compared with placebo patients (0.8%). Increases in ALT and AST ≥3x ULN were reversible with dose modification or treatment discontinuation.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with Esbriet, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) vs placebo (1%). Patients should avoid or minimize exposure to sunlight and sunlamps, regularly use sunscreen (SPF 50 or higher), wear clothing that protects against sun exposure, and avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal (GI) disorders: Patients treated with Esbriet had a higher incidence of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease (GERD), and abdominal pain. GI events required dose reduction or interruption in 18.5% of 2403 mg/day Esbriet-treated patients, compared with 5.8% of placebo patients; 2.2% of 2403 mg/day Esbriet-treated patients discontinued treatment due to a GI event, vs 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modification may be necessary.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, GERD, sinusitis, insomnia, weight decreased, and arthralgia.

Drug Interactions:
CYP1A2 inhibitors: Concomitant use of Esbriet and strong CYP1A2 inhibitors (e.g., fluvoxamine) is not recommended, as CYP1A2 inhibitors increase systemic exposure of Esbriet. If discontinuation of the CYP1A2 inhibitor prior to starting Esbriet is not possible, dosage reduction of Esbriet is recommended. Monitor for adverse reactions and consider discontinuation of Esbriet.

Concomitant use of ciprofloxacin (a moderate CYP1A2 inhibitor) at the dosage of 750 mg BID and Esbriet are not recommended. If this dose of ciprofloxacin cannot be avoided, dosage reductions of Esbriet are recommended, and patients should be monitored.

Moderate or strong inhibitors of both CYP1A2 and other CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

CYP1A2 inducers: Concomitant use of Esbriet and strong CYP1A2 inducers should be avoided, as CYP1A2 inducers may decrease the exposure and efficacy of Esbriet.

Specific Populations:
Mild to moderate hepatic impairment: Esbriet should be used with caution in patients with Child Pugh Class A and B. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

Severe hepatic impairment: Esbriet is not recommended for patients with Child Pugh Class C. Esbriet has not been studied in this patient population.

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WE WON'T BACK DOWN FROM IPF

Help preserve more lung function. Reduce lung function decline.[1–3]

STUDIED IN A RANGE OF PATIENTS

Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications[4]

DEMONSTRATED EFFICACY

In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF[1–4]*

ESTABLISHED SAFETY AND TOLERABILITY

The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[1†]

COMMITTED TO PATIENTS

Genentech offers a breadth of patient support and assistance services to help your patients with IPF[‡]

WORLDWIDE PATIENT EXPERIENCE

More than 42,000 patients have taken pirfenidone worldwide[4§]

Mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} <30 mL/min) renal impairment: Esbriet should be used with caution. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

End-stage renal disease requiring dialysis: Esbriet is not recommended. Esbriet has not been studied in this patient population.

Smokers: Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment and to avoid smoking when on Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

References: 1. Esbriet Prescribing Information. Genentech, Inc. July 2019. **2.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083–2092. **3.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760–1769. **4.** Data on file. Genentech, Inc. 2019.

Learn more about Esbriet and how to access medication at EsbrietHCP.com

IPF=idiopathic pulmonary fibrosis.

*The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).[1] In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide ($\%DL_{co}$) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[2] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[3] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[1,2] Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).[1,3,4] **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.[1,3]**

†Serious adverse reactions, including elevated liver enzymes and drug-induced liver injury, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[1]

‡Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[1]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

ACIP approves 2020 adult vaccination schedule

BY HEIDI SPLETE
MDedge News

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices voted unanimously to approve the adult immunization schedule for 2020, although some fine-tuning may occur before publication.

"Some of the wordsmithing may be done later," ACIP executive secretary Amanda Cohn, MD, said at the ACIP October meeting.

These small changes revolved mainly around how much wording to include in the current color block tables versus including the information in the notes section.

Key updates to the schedule included a change in wording for the definition of the red bars on the table to include "not recommend-

MarianVejcik/Getty Images

ed or contraindicated" instead of only the word "contraindicated." Committee members were especially interested in changing this wording to guide clinicians in use of the live attenuated influenza vaccine because of its potential value in vaccinating health care personnel.

Other updates include language that vaccination of young adults aged 16-23 years who are not at increased risk for meningococcal disease should be vaccinated as follows: "Based on shared clinical decision making, 2-dose series MenB-4C at least 1 month apart or 2-dose series MenB-FHbp at 0, 6 months."

Similarly, clinical decision-making language was added to the notes for the pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13).

The routine vaccination calls for only one dose of PPSV23 given on or after the individual's 65th birthday. Then, based on shared clinical decision making, a dose of PCV13 is recommended for immunocompetent individuals aged 65 years and older. The notes also state that, based on shared clinical decision making, PCV13 and PPSV23 should not be given in the same visit and, if both will be given, PCV13 should be first and should be given 1 year before PPSV23. In addition, "PPSV23 should be given at least 5 years after any previous PPSV23 dose."

"We can't let the perfect be the enemy of the good," said Jason Goldman, MD, liaison representing the ACP. "Those who want to learn the schedule will learn it."

The schedule also adds shared clinical decision making to the notes on human papillomavirus vaccination for adults aged 27-45 years.

The committee members acknowledged the increasing complexity of the adult vaccination schedule, but several members agreed that it is accessible to many clinicians.

"We can't let the perfect be the enemy of the good" said Jason Goldman, MD, liaison representing the American College of Physicians. "Those who want to learn the schedule will learn it; the health system will learn it," even if not every specialist does.

The table "is something to draw you in," said Sandra Fryhofer, MD, an internist who is liaison for the American Medical Association.

More specific information about contraindications for patients with cochlear implants, which also came up in the discussion, may be added to the schedule at a later date.

The ACIP members had no financial conflicts to disclose.

chestphysiciannews@chestnet.org

Guidelines have some weak spots // continued from page 1

- Macrolide monotherapy is only conditionally recommended for outpatients based on resistance levels.
- Procalcitonin assessment, not covered in the 2007 guidelines, is not recommended in order to determine initial antibiotic therapy.
- Corticosteroid use, not covered in the 2007 guidelines, is not recommended, though it may be considered in patients with refractory septic shock.
- The use of health care–associated pneumonia (HCAP) as a category should be dropped, with a switch to an emphasis on local epidemiology and validated risk factors to determine the need for MRSA or *P. aeruginosa* treatment.
- Standard empiric therapy for severe CAP should be beta-lactam/macrolide and beta-lactam/fluoroquinolone combinations, but with stronger evidence in favor of the beta-lactam/macrolide combination.

The updated guidelines include recommendations dealing with the management of patients with comorbidities, and were published in the American Journal of Respiratory and Critical Care Medicine.

"A difference between this guideline and previous ones is that we have significantly increased the proportion of patients in whom we recommend routinely obtaining respiratory tract samples for microbiologic studies. This decision is largely based on a desire to correct the overuse of anti-MRSA and antipseudomonal therapy that has occurred since the introduction of the HCAP classification (which we recommend abandoning) rather than high-quality evidence," the authors concluded. They "expect our move against endorsing monotherapy with macrolides, which is based on population resistance data rather than high-quality clinical studies, will generate future outcomes studies comparing different treatment strategies."Authors reported relationships with pharmaceutical companies; full disclosures are detailed at the end of the guidelines publication.

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SOURCE: Metlay JP et al. Am J Respir Crit Med. 2019;200(7):e45-67.

VIEW ON THE NEWS

From IDWeek 2019: "Ever since we wrote the first CAP [community-acquired pneumonia] guidelines in 1993, we've heard good and bad things, and I agree with both," Michael S. Niederman, MD, FCCP, said in a presentation at IDWeek 2019. "For good or for bad, [guidelines] are a standard against which care can be evaluated." He discussed how, as guidelines have become more evidence based, they have often become "more wishy washy," that when the evidence is weak, the recommendation is weak, and the guidelines merely advise doctors: "You figure it out."

However, he pointed out that, since CAP guidelines were developed, there have been overall improvements in patient care and antibiotic stewardship. But he saw several weaknesses in the new guidelines, including the fact that they did not update minor criteria for determining severe CAP from the 2007 guidelines, despite several studies indicating that there were other criteria to consider. The updated guidelines held a negative view of the use of serum procalcitonin to guide site-of-care decisions, which Dr. Niederman argued went against an analysis of the Etiology of Pneumonia in the Community (EPIC) study.

Dr. Niederman is clinical director of the division of pulmonary and critical care medicine at New York Presbyterian Hospital/Weill Cornell Medical Center, and professor of clinical medicine at Weill Cornell Medical College.

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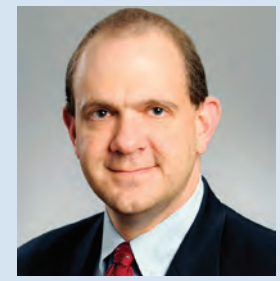

David A. Schulman, MD, FCCP, is Medical Editor in Chief of *CHEST Physician*.

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

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THC identified as probable culprit in vaping injuries, but investigation continues // continued from page 1

and Mortality Weekly report on characteristics of those patients who have died from EVALI-based symptoms as of Oct. 15, 2019.

With data available for more than 867 patients with EVALI, about 86% had a history of using e-cigarette or vaping products that contained THC in the previous 90 days; 64% reported using nicotine-containing products; 34% reported exclusive use of THC-containing products, and 11% reported exclusive use of nicotine-containing products; 52% reported use of both.

In a telebriefing on Oct. 25, Anne Schuchat, MD, CDC principal deputy director, said, "The data do continue to point towards THC-containing products as the source of the vast majority of individuals' lung injury. There are continuing cases that do not report that history. But I'd like to stress that we don't know what the risky material or substance is. THC may be a marker for a way that cartridges were prepared or the way that the devices are producing harm."

EVALI deaths

Among the 29 deaths reported as of Oct. 15, 59% (17) were male. The median age was 45 years (range, 17-75 years), 55 years (range, 17-71 years) among males, and 43 years (range, 27-75 years) among females; the age difference between males and females was not statistically significant. Patients who died tended to be older than patients who survived. Among 19 EVALI patients who died and for whom data on substance use were available, the use of any THC-containing products was reported by patients or proxies for 84% (16), including 63% (12) who exclusively used THC-containing products. Use of any nicotine-containing products was reported for 37% (7), including 16% (3) who exclusively used nicotine-containing products. Use of both THC- and nicotine-containing products was reported in four of those who died.

Investigation update

Mitch Zeller, JD, director, Center for Tobacco Products at the Food and Drug Administration, participated in the telebriefing and provided an update on the ongoing investigation. He said, "FDA has received or collected over 900 samples from 25 states to date. Those numbers continue to increase. The samples [were] collected directly from consumers, hospitals, and from state offices include vaping devices and products that contain liquid as well as packaging and some nearly empty containers." He also noted that the self-reports of THC and/or nicotine use could mean that there are misreported data, because reports in many cases are coming from teens and from jurisdictions in which THC is not legal (see related story on 15).

Dr. Schuchat noted, "We are aware of older cases that look similar to what we are seeing now. But we do not believe that this outbreak or surge in cases is due to better recognition." She suggested that unknown substances may have been introduced into the supply chain.

A "handful" of cases of readmission have been reported, and the CDC is currently investigating whether these cases included patients who took up vaping again or had some other possible contributing factor. Dr. Schuchat cautioned recovering patients not to resume vaping because of the risk of readmission and the probability that their lungs remain in a weakened state.

Clinical guidance update

The CDC provided detailed interim clinical guidance on evaluating and caring for patients with EVALI. The recommendations focus on patient history, lab testing, criteria for hospitalization, and follow-up for these patients.

Obtaining a detailed history of patients presenting with suspected EVALI is especially important for this patient population, given the many unknowns surrounding this condition, according to the CDC. The updated guidance states, "All health care providers evaluating patients for EVALI should ask about the use of e-cigarette or vaping products, and ideally should ask about types of substances used (e.g., THC, cannabis [oil, dabs], nicotine, modified products or the addition of substances not intended by the manufacturer); product source, specific product brand and name; duration and frequency of use, time of last use; product delivery system and method of use (aerosolization, dabbing, or dripping)." The approach recommended for soliciting accurate information is "empathetic, nonjudgmental" and, the guidelines say, patients should be questioned in private regarding sensitive information to ensure confidentiality.

A respiratory virus panel is recommended for all suspected EVALI patients, although at this time, these tests cannot be used to distinguish EVALI from infectious etiologies. All patients should be considered for urine toxicology testing, including testing for THC.

Imaging guidance for suspected EVALI patients includes chest x-ray, with additional CT scan when the x-ray result does not correlate with clinical findings or to evaluate severe or worsening disease.

Recommended criteria for hospitalization of patients with suspected EVALI are those patients with decreased O_2 saturation (less than 95%) on room air, in respiratory distress, or with comorbidities that compromise pulmonary reserve. As of Oct. 8, 96% of patients with suspected EVALI reported to the CDC have been hospitalized.

VCHAL/GETTY IMAGES

As for medical treatment of these patients, corticosteroids have been found to be helpful. The statement noted, "Among 140 cases reported nationally to CDC that received corticosteroids, 82% of patients improved."

The natural progression of this injury is not known, however, and it is possible that patients might recover without corticosteroids. Given the unknown etiology of the disease and "because the diagnosis remains one of exclusion, aggressive empiric therapy with corticosteroids, antimicrobial, and antiviral therapy might be warranted for patients with severe illness. A range of corticosteroid doses, durations, and taper plans might be considered on a case-by-case basis."

The report concluded with a strong recommendation that patients hospitalized with EVALI are followed closely with a visit 1-2 weeks after discharge and again with additional testing 1-2 months later. Health care providers are also advised to consult medical specialists, in particular pulmonologists, who can offer further evaluation, recommend empiric treatment, and review indications for bronchoscopy.

Coding guidance

CDC has issued coding guidance to help track EVALI. The document was posted on the CDC website. The following conditions associated with EVALI are covered in the new coding guidance:

- Bronchitis and pneumonitis caused by chemicals, gases, and fumes; including chemical pneumonitis; J68.0.
- Pneumonitis caused by inhalation of oils and essences; including lipoid pneumonia; J69.1.
- Acute respiratory distress syndrome; J80.
- Pulmonary eosinophilia, not elsewhere classified; J82.
- Acute interstitial pneumonitis; J84.114.

The document notes that the coding guidance has been approved by the National Center for Health Statistics, the American Health Information Management Association, the American Hospital Association, and the Centers for Medicare & Medicaid Services.

The search continues

Mr. Zeller cautioned that this investigation will not be concluded in the near future. He noted, "We are committed to working to [solve the mystery] just as quickly as we can, but we also recognize that it will likely take some time. Importantly, the diversity of the patients and the products or substances they have reported using and the samples being tested may mean ultimately that there are multiple causes of these injuries."

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Richard Franki and Gregory Twachtman contributed to this story.

INNOVATIVE MEDICINE Best Practices

Treatment of Unresectable Stage III Non-small Cell Lung Cancer

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Introduction

With a recent renaissance in cancer diagnostics and treatment, there is renewed promise for many who previously held little hope. Lung cancer represents the second most frequently diagnosed cancer, a close second to breast cancer, at 12.9% of expected new cancer cases in 2019.[1] However, the 23.5% death rate predicted for lung cancer outranks breast, prostate, colorectal, and skin melanomas combined.[1] Five-year lung cancer survival rates have increased from 11% in 1975 to more than 20% in 2016.[1] This relatively low rate of survival can probably be explained by the fact that the majority of patients are diagnosed with locally advanced disease (Stage III, disease metastatic to mediastinal or supraclavicular nodes) or advanced disease (Stage IV, disease metastatic to other organs).[2-4] Recent advancements in treatment are proving effective in improving patient outcomes[5,6]; combined with adherence to screening recommendations and immediate referral to appropriate specialists, earlier diagnosis and staging can help lead to improved outcomes.[7-9]

Non-small cell lung cancer (NSCLC) constitutes 80% to 85% of lung cancer diagnoses, including histological identification of adenocarcinoma, squamous cell, large cell, and undifferentiated carcinomas.[10-12] Approximately 25% to 30% of patients with NSCLC are diagnosed with locally advanced or Stage III disease.[12] A proportion of these patients may experience the curative benefits of combined chemotherapy and surgery or concurrent chemotherapy and radiation therapy.[5,13] About 40% of patients with NSCLC are diagnosed with Stage IV disease, and the treatment goal in these patients is to manage symptoms, improve quality of life, and extend survival.[13,14] Treatment options include systemic chemotherapy, targeted mutation therapies, radiation, immunotherapy, and on occasion surgery.[7] It is vital that we increase early diagnosis, accurate staging, and referral to the appropriate specialists in lung cancer to ensure that treatment is optimized and more lives are potentially saved.[7]

Screening and Diagnosis

Unlike with breast, prostate, and colorectal cancers, systematic screening for lung cancer is not a well-established population-based practice, and its role is not fully grasped by primary caregivers.[15] Risk factors such as history of tobacco use and exposure to second-hand smoke are common knowledge, but other environmental exposures (diesel smoke, pollution, and other cancer-causing agents) are difficult to quantify.[16,17] Populations with lifestyles with higher exposure to these factors are generally more reticent to intervention and skeptical of the benefits of treatment, while others may be concerned that radiation-based screening techniques contribute to the risk.[15] In addition to patient perceptions that defer intervention, presenting symptoms of cough and dyspnea are frequently confounded with other respiratory conditions, creating a delay in early detection and staging.[9] Even further delays have been seen when patients present with more generalized symptoms like fatigue or bone or joint pain.[9]

Based on the National Lung Screening Trial (NLST),[18] the American College of Chest Physicians (ACCP) has published recommendations that low-dose computerized tomography (LDCT) scans be performed annually on patients meeting the following criteria: (1) 30 pack-year current smoker or former smoker between the ages of 55 and 74 years, (2) former smokers who have quit within the past 15 years, and (3) no comorbidities that potentially preclude curative treatment benefit.[15] The National Comprehensive Cancer Network® (NCCN®) also encourages patients to seek yearly screening if they are 50 years or older, have a 20 or more pack-year smoking history, and have other known risk factors besides second-hand smoke exposure, such as radon exposure.[19] Screening with LDCT, in select patients at high risk for lung cancer, decreased the relative risk of death from lung cancer by 20% when compared with chest radiography.[18] As such, efforts are being made to educate general practitioners and the public about this tremendous benefit.[15,19,20]

The goal of screening is to identify a lung cancer in the earliest possible stage, which, as **Table 1** demonstrates, directly improves survivability.[19] However, imaging alone does not provide accurate staging, and once lung cancer is suspected, time is of the essence in ensuring no further progression. Various target time recommendations have been published advocating for improved wait times across the care spectrum, ranging from 30 to 52 days of median wait time from diagnosis to first treatment.[23,24] Yet one Canadian study showed that despite the recommended time of 2 weeks between symptom onset and diagnosis, the actual median time to diagnosis was 4.5 months.[9] It has been estimated that every 4 weeks between scans represents the potential for a 13% progression.[25] Kasymjanova et al describe 2 studies and a meta-analysis demonstrating that increased wait times impart a negative effect on recurrence and survival.[23] In their own study, it was noted that reduced wait times particularly benefited Stage III NSCLC survival.[23]

Because pulmonologists may be the first specialist a patient sees, they are relied upon to diagnose, stage, and coordinate care for many patients with lung cancer.[26] Because Stage III NSCLC is a curative intent setting,[13,27] it is of particular importance to coordinate more complicated surgical, radiation, and chemotherapy care for these patients as soon as the diagnosis and stage have been ascertained.[7] While initial chest computed tomography or positron emission tomography (PET) scans often determine tumor size(s) and location(s), and presence of hilar or mediastinal nodes and extrathoracic lesions (excluding the brain), these studies cannot be the sole factors used in staging, and they falsely overstage 19% of the time and understage 13% of the time.[28] The ACCP guidelines recommend magnetic resonance imaging (MRI) of the brain for patients with clinical Stage III or IV disease with or without symptoms of intracranial disease,[29] whereas NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend staging brain MRI in patients with clinical Stage IB (optional), IIA/B, IIIA/B/C and IV.[30]

Diagnostic procedures to obtain accurate histological diagnosis and staging and adequate tissue samples for molecular testing must be considered, ideally with input from a multidisciplinary team (MDT) composed of pulmonologists, thoracic surgeons, and radiology specialists who are board certified and have expertise in thoracic oncology whenever any stage of NSCLC is suspected.[30] PET imaging can be used to identify the optimal biopsy site that produces the highest yield, is minimally invasive, and is most likely to confer the highest staging.[30] Whenever possible, procedures should be combined (bronchoscopy and endobronchial ultrasound with needle aspiration of lymph nodes) to improve time to diagnosis and clinical staging.[30] Invasive mediastinal staging is recommended before surgical resection.[30] The organization of lung cancer care requires development of a multidisciplinary program committed but not limited to the expeditious coordination of the patient's care among various disciplines to avoid unnecessary tests and procedures, delay in care, costly care, and patient frustration and anxiety.[31] Multidisciplinary care has been shown to decrease time to diagnosis and improve referral for appropriate treatment.[32] In particular, patients with Stage III NSCLC are more

TABLE 1. Summary of NSCLC Staging & Prognosis[3,21,22]

Stage	TNM Classification[21] (Tumor, Node, Metastases)	Nodal Zones & Stations[3,22]		Treatment/Goal[22]	5-Year Survival[21]
IA_1	T1a or T1a(mi), N0, M0			Surgery or radiation	92%
IA_2	T1b, N0, M0			Surgery ± radiation, OR Radiation	83%
IA_3	T1c, N0, M0				77%
IB	T2a, N0, M0			Surgery ± Chemotherapy± Radiation	68%
IIA	T2b, N0, M0				60%
IIB	T1a-c, N1, M0 <or> T2a-b, N1, M0 <or> T3, N0, M0	N1 generally resectable N2 heterogenous resectability	N1 = Hilar Zone if ipsilateral • Station 10 (Hilar nodes) Peripheral Zone if ipsilateral • Station 11 (Interlobar nodes) • Station 12 (Lobar Nodes) • Station 13 (Segmental Nodes) • Station 14 (Subsegmental Nodes		53%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or> T3-4, N1, M0 <or> T4, N1, M0			Surgery ± Chemotherapy ± Radiation	36%
IIIB	T3, N2, M0 <or> T4, N2, M0		N2 = Lower Zone if ipsilateral • Station 8 (Paraesophageal nodes) • Station 9 (Pulmonary ligament nodes) Subcarinal Zone if ipsilateral • Station 7 (Subcarinal nodes) Aortopulmonary Zone • Station 5 (subaortic & aortopulmonary nodes) • Station 6 (para-aortic nodes) Superior Mediastinal Zone • Station 2 (Upper paratracheal nodes) • Station 3 (Prevascular & retrotracheal nodes) • Station 4 (Lower paratracheal nodes)		26%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or>	N2 = heterogenous resectability N3 generally non-resectable		Radiation ± Chemotherapy ± Immunotherapy	36-41%†
IIIB	T1a-c, N3, M0 <or> T2a-b, N3, M0 <or> T3, N2, M0 <or> T4, N2, M0		N3 = Supraclavicular Zone • Station 1 (Low cervical, supraclavicular, sternal notch nodes • contralateral mediastinal, contralateral hilar, ipsilateral/contralateral scalene, superclavicular nodes	Radiation ± Chemotherapy ± Immunotherapy	24-26%†
IIIC	T3-4, N3, M0				12-13%†
IVA	Any T, Any N, M1a-b			Palliative Care with Systemic Therapy	0%
IVB	Any T, Any N, M1c				0%

Abbreviations: M1a, separate tumor contralateral lobe or primary tumor with pleural/pericardial nodules or malignant effusions; M1b, single extrathoracic mass; M1c, multiple extrathoracic masses; mi, minimally invasive adenocarcinoma.
T1a ≤ 1cm; T1b >1cm, ≤ 2cm; T1c >2cm, ≤ 3cm; T2a >3cm, ≤ 3cm; T2b >4cm, ≤ 5cm; T3 >5cm, ≤ 7cm; T4 >7cm.
†Reflects changes in 5-year survival of all stage III NSCLC when staging included pathology information.

likely to receive appropriate treatment when referred to oncology specialists.[7] Still, data suggest that up to 20% of patients diagnosed with Stage III NSCLC are never evaluated by an oncologist.[33]

The tumor, node, metastasis (TNM) system for staging has been used since 1944.[8] Now governed by the International Association for the Study of Lung Cancer (IASLC), the eighth edition took effect in 2017.[21] Several changes from the seventh edition, including new TNM definitions and addition of categories, have caused shifts in staging, with a greater emphasis on tumor size and invasion of surrounding tissues.[3] As a result, Stage III now includes subtype C (T3-T4, N3, M0), which is still treated in a curative intent setting.[21] Additionally, nodal zones were further broken down into more specific stations that clearly define anatomic landmarks within each zone, as this too proved to be associated with prognosis.[3] Differentiating Stage IIIC from Stage IVA has provided more patients the opportunity to be treated in a curative intent setting, as further data collection and new research are expanding within each subtype and allowing for individualized treatment approaches.[3,21]

Clinically, the distinction between resectable and unresectable Stage III disease is of significance because unresectable Stage III does not afford a treatment path as well-established as resectable disease (surgery).[34] Unresectable generally includes Stage IIIA tumors (T1-T2 tumors with multiple positive ipsilateral mediastinal notes), often described as bulky or extensive; Stage IIIB (T1-T2 tumors with positive contralateral mediastinal or supraclavicular nodes or T3-T4 tumors with positive ipsilateral mediastinal nodes); and Stage IIIC (T3-T4 tumors with positive contralateral mediastinal or supraclavicular nodes).[11]

Treatment of Stage III NSCLC

Patients clinically determined to have resectable Stage III NSCLC are candidates for a variety of treatment options, none of which have proven to be superior.[11] The 2019 NCCN Guidelines® suggest the following course for resectable Stage III NSCLC: (1) Preoperative chemotherapy (CT) and radiation (CTR), or preoperative CT followed by postoperative RT (split-panel decision); and (2) surgery, using minimally invasive techniques where possible.[30] The panel acknowledges that controversy remains regarding the sequencing of surgery, chemotherapy, and radiation techniques.

The majority of patients with Stage III NSCLC have unresectable disease.[35] Platinum-based CT has been preferred over other chemotherapeutic modalities for over 3 decades.[36] Evidence supports its use as part of definitive CRT along with a minimum of 60 Gy in escalated doses; concurrent treatment is currently preferred over sequential in all histological findings.[30] Accelerated RT alone imparts some benefit to those who refuse CT.[11]

Severe immune-mediated adverse reactions are associated with all immune checkpoint inhibitors, including pneumonitis, causing discontinuation.[37] A recent retrospective single-center study suggests that patients who are on corticosteroids for cancer-unrelated indications have similar outcomes on immunotherapy as patients who are receiving 0 to < 10 mg of prednisone.[37] However, additional mechanistic studies as well as prospective clinical trials are needed to identify whether the use of corticosteroids affects specific aspects of the immune system necessary for immunotherapy activity. Optimal treatment duration for immune checkpoint inhibitors requires further study, and their use in patients with autoimmune disorders and a past organ transplantation should be avoided.[38]

Conclusion

Locally advanced and metastatic NSCLC patients have benefitted from intensive research into immunologic approaches to treatment. Accurate diagnosis and staging are critical, particularly in the differentiation between Stage III, which is treated with curative intent, and Stage IV, which is metastatic. CRT is the current standard of care for unresectable Stage III disease and has shown improvement in overall survival, while the introduction of immunotherapy following CRT treatment can be discussed as a treatment option. To reap the benefits of these advances in treatment, patients with suspected or confirmed lung cancer should be managed by an MDT that includes a pulmonologist, thoracic surgeon, and medical and radiation oncologists, and referral for appropriate treatment of Stage III and IV NSCLC is crucial to improving patient outcomes.

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Dupilumab shrinks nasal polyps in severe chronic rhinosinusitus

BY TED BOSWORTH
MDedge News

MADRID – In adults with severe chronic rhinosinusitus with nasal polyps (CRSwNP), the monoclonal antibody dupilumab is effective for shrinking the polyps, improving symptoms, and reducing the need for systemic corticosteroids and surgery, according to results of two phase 3 studies reported together at the annual congress of the European Respiratory Society.

"Dupilumab improved all of the disease components, and the improvement was observed in most of them at the first assessment," reported Jorge F. Máspero, MD, research director, Fundacion Cidea, Buenos Aires.

The data were drawn from multicenter phase 3 trials called LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52. Both included stratifications for asthma and for NSAID-exacerbated respiratory disease (ERD), which are common comorbidities. Findings of the two studies were published together just prior to Dr. Máspero's presentation at the ERS (Lancet. 2019 Sep 26. doi: 10.1016/S0140-6736[19]31881-1).

For the coprimary end point of endoscopic nasal polyp score (NSP), the reductions were 2.06 and 1.8 at 24 weeks from baseline (both *P* less than .0001) in SINUS-24 and SINUS-52, respectively. For the nasal congestion or obstruction score, another primary end point, the reductions were 0.89 and 0.87, respectively (both *P* less than .0001).

There were also major improvements at week 24 on secondary end points, including the Lund-McKay CT score for staging of CRSwNP (*P* less than .0001), total symptom score (*P* less than .0001), the UPSIT test for smell (*P* less than .0001), and SNOT-22 (*P* less than .0001), a quality of life instrument specific for nasal and sinus diseases.

When these outcomes were graphed, curves for the dupilumab and placebo arms had already separated by 4 weeks, "and then we see the dupilumab patients keep getting better over the course of follow-up, and the effect was seen regardless of comorbidities," said Dr. Máspero, referring to concomitant asthma or ERD.

The SINUS-24 trial randomly assigned 276 CRSwNP patients to 300 mg dupilumab or placebo, each given subcutaneously every 2 weeks. The SINUS-52 trial, which randomized 448 patients, included the same two arms plus a third arm in which patients also received 300 mg dupilumab every 2 weeks for 24 weeks and then 300 mg every month for an additional 26 weeks.


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Dr. Jorge F. Máspero

In a pooled analysis of these trials, patients randomized to dupilumab had a 78% reduction in likelihood of receiving systemic corticosteroids and a 79% reduction in being referred for surgery relative to placebo, Dr. Máspero reported.

Dupilumab, a monoclonal antibody that inhibits the activity of interleukin-4, IL-5, and IL-13, was well tolerated. Among the most common adverse events, there were lower rates of headache (9% vs. 7%), epistaxis (7% vs. 6%), and injection-site erythema (8% vs. 6%) in the dupilumab and placebo arms, respectively, but the rate of serious adverse events (6% vs. 3%) and adverse events leading to treatment discontinuation (5% vs. 3%) were only slightly higher in the active-treatment group.

Both trials, which required a bilateral baseline NPS score of 5.0 for entry, recruited a population with relatively severe CRSwNP, according to Dr. Máspero. Of the 724 patients, 204 had ERD.

A restored sense of smell was one of the contributors to an improvement in quality of life.

"The sense of smell improves very quickly after starting dupilumab. Patients reported results within 2 weeks, and there was an almost complete lack of improvement in the placebo group," Dr. Máspero reported.

Dupilumab is already indicated for the treatment of CRSwNP, but this study confirms a major effect on polyp size, sinus congestion, and symptoms irrespective of the presence of common comorbidities affecting the airways, Dr. Máspero said.

Dr. Maspero reports no potential conflicts of interest.

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SOURCE: Bachert C et al. Lancet. 2019 Sep 26. doi: 10.1016/S0140-6736(19)31881-1.

In-hospital flu shot curbed readmissions in patients with CAP

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – In-hospital flu shots were rare, yet linked to a lower readmission rate for patients hospitalized with community-acquired pneumonia in a recent retrospective study, suggesting a "missed opportunity" to improve outcomes for these patients, an investigator said.

Less than 2% of patients admitted for community-acquired pneumonia (CAP) received in-hospital influenza vaccination, yet receiving it was linked to a 20% reduction in readmissions, according to investigator Kam Sing Ho, MD, a resident at Mount Sinai St. Luke's, New York.

Those patients who were readmitted had a significantly higher death rate vs. index admissions, Dr. Ho said in a poster discussion session at the annual meeting of the American College of Chest Physicians.

"I know (vaccines) are pretty much pushed out to the outpatient setting, but given what we showed here in this abstract, I think there's a role for influenza vaccines to be a discussion in the hospital," Dr. Ho said in his presentation.

The retrospective analysis was based on 825,906 adult hospital admissions with a primary diagnosis of CAP in data from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP). Of that large cohort, just 14,047 (1.91%) received in-hospital influenza vaccination, according to Dr. Ho.

In-hospital influenza vaccination independently predicted a lower risk of readmission (hazard ratio, 0.821; 95% confidence interval, 0.69-0.98; *P* less than .02) in a propensity score – matching analysis that included 9,777 CAP patients who received the vaccination and 9,777 with similar demographic and clinical characteristics.

Private insurance and high-income status also predicted lower risk of readmission in the analysis, while by contrast, factors associated with higher risk of readmission included advanced age, Medicare insurance, and respiratory failure, among other factors, Dr. Ho reported.

The overall 30-day rate of readmission in the study was 11.9%, and of those readmissions, the great majority (about 80%) were due to pneumonia, he said.

The rate of death in the hospital was 2.96% for CAP patients who were readmitted, versus 1.11% for the index admissions (*P* less than .001), Dr. Ho reported. Moreover, readmissions were associated with nearly half a million hospital days, $1 billion in costs, and $3.67 billion in charges.

Based on these findings, Dr. Ho and colleagues hope to incorporate routine influenza vaccination for all adults hospitalized with CAP.

"We're always under pressure to do so much for patients that we can't comprehensively do everything. But the 20% reduction in the risk of coming back, I think that's significant," Dr. Ho said in an interview.

The authors reported having no disclosures related to this research.

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SOURCE: Ho KS et al. CHEST 2019. Abstract doi: 10.1016/j.chest.2019.08.450.

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Recent COPD exacerbation did not affect aclidinium's efficacy in high-risk patients

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – A history of recent exacerbations did not significantly affect the safety or efficacy of aclidinium bromide (Tudorza) in patients with moderate to severe chronic obstructive pulmonary disease and high cardiovascular risk, analysis of a postmarketing surveillance trial suggests.

Regardless of exacerbation history, the long-acting muscarinic antagonist reduced the rate of moderate or severe COPD exacerbations versus placebo in this subgroup analysis of the phase IV ASCENT-COPD trial, presented here at the annual meeting of the American College of Chest Physicians.

At the same time, there were no significant increases in the risk of mortality or major adverse cardiac events (MACE) for those patients who had an exacerbation in the past year versus those who did not, according to investigator Robert A. Wise, MD.

ANDREW D. BOWSER/MDEDGE NEWS

Dr. Robert A. Wise

Those findings may be reassuring, given that COPD patients commonly have comorbidities and cardiovascular risk factors, according to Dr. Wise, professor of medicine at the Johns Hopkins University, Baltimore.

"There's a concern and some evidence that patients who have a propensity to COPD exacerbations may also have an increased risk for cardiovascular events," Dr. Wise said in a podium presentation.

Accordingly, he and coinvestigators sought to tease out the impact of COPD exacerbations on safety as well as efficacy in the randomized, placebo-controlled ASCENT-COPD trial, which included 3,630 patients with moderate to severe COPD plus a cardiovascular disease history or multiple atherothrombotic risk factors.

Of the patients who were analyzed in the study, 1,433 patients had at least one treated COPD exacerbation in the year before screening for the study, while 2,156 had no exacerbations in the prior year, Dr. Wise said.

Top-line results of that study, published several months ago, showed that aclidinium did not increase MACE risk over 3 years, and reduced the rate of moderate to severe COPD exacerbations over the first year (JAMA. 2019 7 May 7;321[17]:1693-701).

In this latest analysis, presented at the meeting, risk of MACE with aclidinium treatment was not increased versus placebo, irrespective of whether they had exacerbations in the prior year (interaction $P = .233$); likewise, the risk of all-cause mortality was similar between groups ($P = .154$).

In terms of reduction in moderate or severe COPD exacerbations in the first year, aclidinium was superior to placebo both for the patients who had at least one exacerbation in the prior year (rate ratio, 0.80) and those who had no exacerbations in the prior year (RR, 0.69).

"This translates into a number needed to treat to prevent one exacerbation of about 11 patients for those without an exacerbation, compared to about 6 patients for those with a prior exacerbation," Dr. Wise said in his presentation.

The ASCENT-COPD study was funded initially by Forest Laboratories and later by AstraZeneca and Circassia. Dr. Wise provided disclosures related to AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Sunovion, Mylan/Theravance, Contrafect, Pearl, Merck, Verona, Novartis, AbbVie, Syneos, Regeneron, and Kiniksa.

SOURCE: Wise RA et al. CHEST 2019 Abstract doi: 10.1016/j.chest.2019.08.231.

Race mismatch may affect survival in lung transplant setting

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – Race compatibility is a factor that can affect survival and needs to be considered when matching lung transplant candidates to potential donors, results from a large retrospective analysis suggest.

Specifically, whites had significantly worse survival when receiving lungs from African American donors in this registry analysis, according to study investigator Alexis Kofi Okoh, MD.

By contrast, donor-to-recipient race compatibility (DRRC) did not affect posttransplant survival among African American or Hispanic patients, said Dr. Okoh, who is with the lung transplant division at the Rutgers Robert Wood Johnson Medical School, New Brunswick, N.J.

While race mismatch has been shown to affect outcomes in kidney, heart, and liver transplant settings, the data for DRRC in lung transplant prior to this analysis generally have been limited to small, single-center studies, according to Dr. Okoh.

"If you do have the option, [race compatibility] should highly be considered, because it clearly has an impact on outcomes," Dr. Okoh said in an interview here at the annual meeting of the American College of Chest Physicians.

Considering the race of both donor and recipient is especially important now that the lung transplant population is becoming more ethnically diverse, he added.

The study was based on an analysis of 19,504 lung transplant recipients in the prospectively maintained United Network for Organ Sharing (UNOS) database during 2006-2018. In that cohort, 16,485 recipients were white, 1,787 were African American, and 1,232 were Hispanic.

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Dr. Alexis Kofi Okoh

Race-matched donor organs were used in two-thirds (66.2%) of white recipients, about one-quarter (26.8%) of African American recipients, and one-third (33.0%) of Hispanic recipients.

Overall, survival post–lung transplant was significantly poorer among recipients who did not receive a race-matched organ in Kaplan-Meier survival estimates. Dr. Okoh said that this effect was diminished after they adjusted for patient baseline characteristics ($P = 0.2809$).

For African American recipients, the unadjusted and adjusted survival estimates were no different regardless of donor race, and likewise, there were no apparent survival differences between Hispanic recipients who received race matched or mismatched organs.

Survival among white recipients, however, was significantly affected by race of the recipient, with decreased survival estimates noted even after adjustment for patient characteristics, according to Dr. Okoh's presentation.

Results of regression analysis showed that white recipient/African American donor was the only race mismatch to significantly affect survival, Dr. Okoh said in the interview.

The posttransplant survival hazard ratios (and 95% confidence intervals) reported by Dr. Okoh with a no race mismatch serving as reference were 1.15 (1.08-1.23) for whites with African American donors, and 1.09 (1.01-1.18) for Whites with Hispanic donors.

Dr. Okoh and coinvestigators reported no relevant conflicts in relation to their study.

SOURCE: Okoh AK et al. CHEST 2019 Abstract doi: 10.1016/j.chest.2019.08.220.

FDA approves elexacaftor/ivacaftor/tezacaftor for CF

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has approved elexacaftor/ivacaftor/tezacaftor (Trikafta) for the treatment of the most common type of cystic fibrosis in patients aged 12 years or older, the first triple-combination therapy approved for that indication.

Approval for Trikafta was based on results from two clinical trials in patients with cystic fibrosis with an F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. In the first trial, a 24-week, randomized, double-blind, placebo-controlled study of 403 patients, the mean percent predicted forced expiratory volume in 1 second increased by 14% from baseline, compared with placebo. In the second trial, a 4-week, randomized, double-blind, active-controlled study of 107 patients, mean percent predicted forced expiratory volume in 1 second was increased 10% from baseline, compared with tezacaftor/ivacaftor, according to the FDA press release.

Approval for the combination was based on results from two clinical trials in patients with cystic fibrosis with an F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

In the first trial, patients who received Trikafta also saw improvement in sweat chloride, reduction in the number of pulmonary exacerbations, and reduction of body mass index, compared with placebo.

The most common adverse events associated with Trikafta during the trials were headaches, upper respiratory tract infections, abdominal pains, diarrhea, rashes, and rhinorrhea, among others. The label includes a warning related to elevated liver function tests, use at the same time with products that induce or inhibit a liver enzyme called cytochrome P450 3A4, and cataract risk.

"At the FDA, we're consistently looking for ways to help speed the development of new therapies for complex diseases, while maintaining our high standards of review. Today's landmark approval is a testament to these efforts, making a novel treatment available to most cystic fibrosis patients, including adolescents, who previously had no options and giving others in the cystic fibrosis community access to an additional effective therapy," said acting FDA Commissioner Ned Sharpless, MD.

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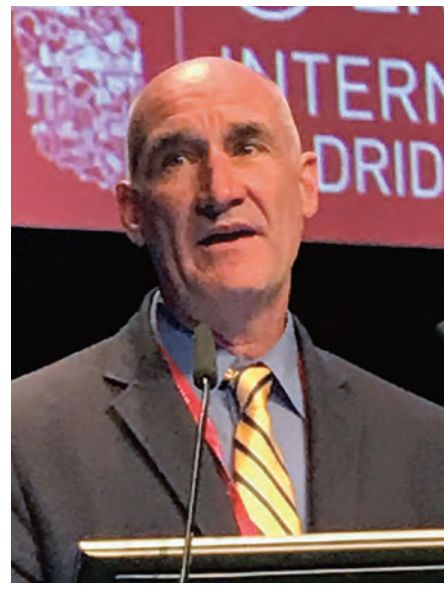
TKI preserved lung function in patients with fibrosing pulmonary disease

BY TED BOSWORTH
MDedge News

MADRID – In patients with fibrosing lung diseases other than idiopathic pulmonary fibrosis (IPF), nintedanib, a tyrosine kinase inhibitor (TKI), substantially reduced the rate of decline in lung function, according to findings from a phase 3, placebo -controlled trial presented at the annual congress of the European Respiratory Society.

The trial, called INBUILD, enrolled patients who had a progressive lung disease with a fibrosing phenotype, such as interstitial pneumonia with autoimmune features or noninterstitial pneumonia, on the premise that these conditions might share a pathology responsive to a common therapy, explained Kevin R. Flaherty, MD, of National Jewish Health, Denver. The INBUILD trial was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at 153 sites in 15 countries. A total of 663 patients underwent randomization and received at least one dose of nintedanib (332) or placebo (331).



Ted Bosworth/MDedge News

Dr. Kevin R Flaherty

Patients with fibrosing lung disease affecting more than 10% of lung volume were randomized to 150 mg twice daily of nintedanib, which inhibits intracellular growth factors implicated in fibrosis and is already indicated for IPF, or matching placebo.

On the primary endpoint of change in forced vital capacity (FVC) at 52 weeks, those in the nintedanib arm lost lung function at a rate that was less than half that of those randomized to placebo (–80.8 vs. –187.8 mL/year; *P* less than .001).

In a preplanned stratification, the protection from nintedanib against a decline in lung function was found to be at least as good in those with a usual interstitial pneumonia (UIP-like) pattern of fibrosis on baseline imaging (–82.9 vs. –211.1 mL/year), compared with those with other fibrotic patterns (–79.0 vs. –154.2 mL/year). The UIP-like subgroup represented about 60% of those enrolled.

"The relative protection from decline in lung function supports the hypothesis that progressive fibrosing interstitial lung diseases have a similar pathobiologic mechanism," said Dr. Flaherty. Results from the INBUILD were published simultaneously with his ERS presentation (N Engl J Med. 2019 Sep 29. doi: 10.1056/NEJMoa1908681).

The curves documenting change of lung function in favor of nintedanib relative to placebo separated within 12 weeks of treatment initiation, according to Dr. Flaherty. The ERS-invited discussant, Martin Kolb, MD, PhD, professor of respirology, McMaster University, Hamilton, Ont., called the reductions in loss of lung function "profound" and "very impactful."

However, despite these reductions, there was no significant difference in quality of life as measured with the King's Brief Interstitial Lung Disease (KBILD) questionnaire, which was a secondary outcome. The problem was that there was little change in KBILD in either group at 52 weeks, limiting the ability to show differences.

"The relative protection from decline in lung function supports the hypothesis that progressive fibrosing interstitial lung diseases have a similar pathobiologic mechanism."

The rates of death were numerically lower at 52 weeks in the nintedanib arm for the study overall (4.8% vs. 5.1%) and for the UIP-like subgroup (5.3% vs. 7.8%), but the differences did not reach statistical significance.

A suggestion of benefit was derived from a design feature of INBUILD that called for patients to remain on blinded therapy until all enrolled patients completed the trial. When the effect of nintedanib was evaluated in this extended analysis, the event curves for the combined endpoint of interstitial lung disease or death separated and approached significance.

In this extended analysis, which

Continued on following page

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: One of the most noticeable continuing voids in pulmonary medicine is the lack of effective therapy for some patients with non-IPF interstitial lung disease. The morbidity and mortality associated with these conditions often mirror those of IPF, and anything that potentially could improve patients' lives and outlook would be highly welcomed. This study of nintedanib provides exciting data suggesting its effectiveness in reducing the rate of lung function decline in these conditions – with reductions similar to those demonstrated in IPF patients. Similar to the initial IPF studies, this study failed to show a statistically significant decline in mortality versus placebo – although they report a trend that with extended use this may show significance, and further study is needed in this regard. Finally, it is notable that approximately 20% of patients discontinued the drug due to side effects (mostly GI) – which may limit its use somewhat but also may suggest an even larger-than-mean effect in patients able to tolerate it long term.

New guideline conditionally recommends long-term home NIV for patients with COPD

BY STEVE CIMINO
MDedge News

Long-term home noninvasive ventilation (LTH-NIV) has conditional value for patients with chronic hypercapnic chronic obstructive pulmonary disease (COPD), according to a new guideline from a European Respiratory Society task force.

"Our recommendations, based on the best available evidence, can guide the management of chronic hypercapnic respiratory failure in COPD patients aimed at improving patient outcomes," wrote Begum Ergan, MD, of Dokuz Eylul University, Izmir, Turkey, and coauthors. The guideline was published in the European Respiratory Journal.

To provide insight into the clinical application of LTH-NIV, the European Respiratory Society convened a task force of 20 clinicians, methodologists, and experts. Their four recommendations were developed based on the GRADE (Grading, Recommendation, Assessment, Development and Evaluation) methodology.

The first recommendation was to use LTH-NIV for patients with chronic stable hypercapnic COPD. Though an analysis of randomized, controlled trials showed little effect on mortality or hospitalizations, pooled analyses showed that NIV may decrease dyspnea scores (standardized mean difference, –0.51; 95% confidence interval, –0.06 to –0.95) and increase health-related quality of life (SMD, 0.49; 95% CI, –0.01 to 0.98).

The second was to use LTH-NIV in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists. Though it was not associated with a reduction in mortality (risk ratio, 0.92; 95% CI, 0.67-1.25), it was found to potentially reduce exacerbations (SMD, 0.19; 95% CI, –0.40 to 0.01) and hospitalizations (RR, 0.61; 95% CI, 0.30-1.24).

The third was to titrate LTH-NIV to normalize or reduce $PaCO_2$ levels in patients with COPD. While this recommendation was issued with a very low certainty of evidence, it was driven by the "minimal potential harms of targeted $PaCO_2$ reduction."

The fourth was to use fixed pressure support mode as first-choice ventilator mode in patients with COPD using LTH-NIV. The six trials on this subject did not provide insight into long-term outcomes, nor were there significant improvements seen in health-related quality of life, sleep quality, or exercise tolerance. As such, it was also issued with a very low certainty of evidence.

The authors acknowledged all four recommendations as weak and conditional, "due to limitations in the certainty of the available evidence." As such, they noted that their recommendations "require consideration of individual preferences, resource considerations, technical expertise, and clinical circumstances prior to implementation in clinical practice."

The authors reported numerous disclosures, including receiving grants and personal fees from various medical supply companies.

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SOURCE: Ergan B et al. Eur Respir J. 2019 Aug 29. doi: 10.1183/13993003.01003-2019.

Continued from previous page

suggests that clinical benefit is likely to accrue after longer periods of treatment, "we saw similar trends when we looked at mortality as an independent outcome," Dr. Flaherty reported.

More patients in the nintedanib group discontinued therapy because of adverse events (19.6% vs. 10.3%), but Dr. Flaherty characterized the rate of serious adverse events as "similar." He made this statement even though several adverse events, particularly those involving the gastrointestinal tract, such as diarrhea (66.9% vs. 23.9%), nausea (28.9% vs. 9.4%), vomiting (18.4% vs. 5.1%), and abdominal pain (10.2% vs. 2.4%), were higher in the nintedanib arm.

The INBUILD trial demonstrates that nintedanib preserves lung function in fibrosing lung diseases other than IPF. In his review of this paper, Dr. Kolb pointed out that non-IPF etiologies represent about 75% of interstitial lung diseases. For these patients "we have no drugs, so there is a big medical need."

Dr. Flaherty reports no potential conflicts of interest. The study was funded by Boehringer-Ingelheim, which produces nintedanib.

chestphysiciannews@chestnet.org

SOURCE: Flaherty KR et al. N Engl J Med. 2019 Sep 29. doi: 10.1056/NEJMoa1908681.

Histologic analysis of vaping-associated lung injury suggests chemical pneumonitis

BY LUCAS FRANKI
MDedge News

VLADEE/GETTY IMAGES

Vaping-associated lung injury is likely a form of airway-centered chemical pneumonitis, not exogenous lipoid pneumonia, according to Yasmeen M. Butt, MD, of the University of Texas Southwestern Medical Center, Dallas, and associates.

Dr. Butt and associates performed a review of lung biopsies from 17 patients (13 men; median age, 35 years) with a history of vaping and either suspected or confirmed vaping-associated lung injury. All cases showed patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, or organizing pneumonia, the authors noted in a letter to the editor published in the New England Journal of Medicine.

While no histologic findings were specific, foamy macrophages and pneumocyte vacuolization were seen in all cases, the authors added. Pigmented macrophages were occasionally present but not dominant, neutrophils were often prominent, eosinophils were rare, and granulomas were not seen. Two patients eventually died, despite treatment with glucocorticoids and maximum supportive care.

"None of our cases showed histologic evidence of exogenous lipoid pneumonia and no radiologic evidence thereof has been found; this calls into question the diagnostic utility of identifying lipid-laden macrophages or performing oil red O staining on bronchioloalveolar lavage fluid as a marker of vaping-associated lung injury, as has been proposed," Dr. Butt and associates wrote.

No conflicts of interest were reported.

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SOURCE: Butt YM et al. N Engl J Med. 2019 Oct 2. doi: 10.1056/NEJMc1913069.

Instead of choosing an ICS/LABA,

START BREAKING TRADITION

Start appropriate symptomatic patients with COPD on ANORO for dual bronchodilation

The GOLD 2019 Report

- **Continues to emphasize the role of LAMA/LABA for patients with COPD**[1]
- **Does not include ICS/LABA as initial treatment for many patients**[1]

ANORO was studied in patients with moderate or worse COPD.

INDICATION

ANORO is for the maintenance treatment of patients with COPD. ANORO is NOT for the relief of acute bronchospasm or for asthma.

Important Safety Information

CONTRAINDICATIONS

- ANORO is contraindicated in patients with severe hypersensitivity to milk proteins or with hypersensitivity to umeclidinium, vilanterol, or any of the excipients.
- Use of a long-acting beta$_2$-adrenergic agonist (LABA) without an inhaled corticosteroid (ICS) is contraindicated in patients with asthma.

WARNINGS AND PRECAUTIONS

- The safety and efficacy of ANORO in patients with asthma have not been established. ANORO is not indicated for the treatment of asthma. Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. Available data do not suggest an increased risk of death with use of LABA in patients with COPD.
- ANORO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.
Please see Brief Summary of Prescribing Information for ANORO ELLIPTA following this ad.

START WITH ANORO FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION VS AN ICS/LABA[2]

Nearly 2x the lung function improvement vs ADVAIR[2]

LS mean change from baseline in weighted mean FEV_1 (0-24 hours) on Day 84

1.8x IMPROVEMENT

Study DB2114930[2]

74-mL Difference (*P*<0.001)
ANORO **165 mL (n=353)**
ADVAIR **91 mL (n=353)**

1.9x IMPROVEMENT

Study DB2114951[2]

101-mL Difference (*P*<0.001)
ANORO **213 mL (n=349)**
ADVAIR **112 mL (n=348)**

Studied in patients with moderate to severe COPD (GOLD 2 or 3).[2]

What would almost 2x the lung function improvement mean for your patients?

Learn more at StartWithANORO.com

Description of studies[2,3]: The efficacy and safety of a once-daily dose of ANORO ELLIPTA and a twice-daily dose of ADVAIR DISKUS 250 mcg/50 mcg were evaluated in 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group studies in patients (mean age range: 63 to 64 years) with COPD with no exacerbations (COPD symptoms requiring oral corticosteroids, antibiotics, and/or hospitalization) in the previous year. At screening, patients had a mean postbronchodilator FEV_1 range of 49.4% to 49.5% predicted. The studies were not powered to compare the safety profiles of the products.

Primary endpoint: Weighted mean FEV_1 (0-24 hours postdose) on Day 84.

COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist; LS=least squares.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ANORO should not be used more often or at higher doses than recommended or with another LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO. Discontinue ANORO if such reactions occur.

ANORO ELLIPTA
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO may need to be discontinued. ANORO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors as increased systemic exposure to vilanterol and cardiovascular adverse effects may occur. See prior Warning and Precaution regarding CYP3A4 inhibitors.
- ANORO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Please see additional Important Safety Information for ANORO ELLIPTA on the previous pages.
Please see Brief Summary of Prescribing Information for ANORO ELLIPTA following this ad.

References: 1. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. 2019 report. www.goldcopd.org. Accessed November 27, 2018. **2.** Donohue JF, Worsley S, Zu C-Q, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med.* 2015; 109(7):870-881. **3.** Data on file, GSK.

Visit StartWithANORO.com

ANORO ELLIPTA
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

ANORO ELLIPTA was developed in collaboration with INNOVIVA

UCVADVT190009 August 2019
Produced in USA.

BRIEF SUMMARY

ANORO ELLIPTA
(umeclidinium and vilanterol inhalation powder), for oral inhalation use

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE
ANORO ELLIPTA is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).
Important Limitations of Use
ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma. The safety and efficacy of ANORO ELLIPTA in asthma have not been established.
4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full prescribing information]*.
Use of a long-acting $beta_2$-adrenergic agonist (LABA) without an inhaled corticosteroid (ICS) is contraindicated in patients with asthma *[see Warnings and Precautions (5.1)]*. ANORO ELLIPTA is not indicated for the treatment of asthma.
5 WARNINGS AND PRECAUTIONS
5.1 Serious Asthma-Related Events—Hospitalizations, Intubations, Death
The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established.
ANORO ELLIPTA is not indicated for the treatment of asthma *[see Contraindications (4)]*.
Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted.
Available data do not suggest an increased risk of death with use of LABA in patients with COPD.
5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use with Other Long-acting $Beta_2$-agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO ELLIPTA. Discontinue ANORO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full prescribing information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
In a 52-week trial of subjects with COPD, the exposure-adjusted rates for any on-treatment major adverse cardiac event, including non-fatal central nervous system hemorrhages and cerebrovascular conditions, non-fatal myocardial infarction, non-fatal acute myocardial infarction, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per 100 patient-years for fluticasone furoate/umeclidinium/vilanterol 100 mcg/62.5 mcg/25 mcg (n = 4,151), 1.9 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg (n = 4,134), and 2.2 per 100 patient-years for ANORO ELLIPTA (n = 2,070). Adjudicated on-treatment deaths due to cardiovascular events occurred in 20 of 4,151 patients (0.54 per 100 patient-years) receiving fluticasone furoate/umeclidinium/vilanterol, 27 of 4,134 patients (0.78 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 16 of 2,070 patients (0.94 per 100 patient-years) receiving ANORO ELLIPTA.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients.
In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.
6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Serious asthma-related events–hospitalizations, intubations, death. LABA, such as vilanterol (one of the active ingredients in ANORO ELLIPTA), as monotherapy (without ICS) for asthma increase the risk of asthma-related events. ANORO ELLIPTA is not indicated for the treatment of asthma [*see Warnings and Precautions (5.1)*].
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and two 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials
The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trial 1, NCT #01313650 and Trial 2, NCT #01313637); N = 1,532 and N = 1,489, respectively) and 2 active-controlled trials (Trial 3, NCT #01316900 and Trial 4, NCT #01316913); N = 843 and N = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%).
Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.
Table 1. Adverse Reactions with ANORO ELLIPTA with ≥1% Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %	Placebo (n = 555) %
Infections and infestations				
Pharyngitis	2	1	2	<1
Sinusitis	1	<1	1	<1
Lower respiratory tract infection	1	<1	<1	<1
Gastrointestinal disorders				
Constipation	1	<1	<1	<1
Diarrhea	2	<1	2	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	2	<1	2	1
Muscle spasms	1	<1	<1	<1
Neck pain	1	<1	<1	<1
General disorders and administration site conditions				
Chest pain	1	<1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence <1% but more common than placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trials
In a long-term safety trial (Trial 5, NCT #01316887), 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions observed with a frequency of ≥1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.
6.2 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of ANORO ELLIPTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ANORO ELLIPTA or a combination of these factors.
Cardiac Disorders
Palpitations.
Eye Disorders
Blurred vision, glaucoma, increased intraocular pressure.
Immune System Disorders
Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.
Nervous System Disorders
Dysgeusia, tremor.
Psychiatric Disorders
Anxiety.
Renal and Urinary Disorders
Dysuria, urinary retention.
Respiratory, Thoracic, and Mediastinal Disorders
Dysphonia, paradoxical bronchospasm.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women to inform a drug-associated risk. *(See Clinical Considerations.)* In animal reproduction studies, umeclidinium administered via inhalation or subcutaneously to pregnant rats and rabbits was not associated with adverse effects on embryofetal development at exposures approximately 50 and 200 times, respectively, the human exposure at the maximum recommended human daily inhaled dose (MRHDID). Vilanterol administered via inhalation to pregnant rats and rabbits produced no fetal structural abnormalities at exposures approximately 70 times the MRHDID. *(See Data.)*

The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Labor and Delivery: There are no human studies evaluating the effects of ANORO ELLIPTA, umeclidinium, or vilanterol during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of ANORO ELLIPTA during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Data

Animal Data: The combination of umeclidinium and vilanterol has not been studied in pregnant animals. Studies in pregnant animals have been conducted with umeclidinium and vilanterol individually.

Umeclidinium: In separate embryofetal developmental studies, pregnant rats and rabbits received umeclidinium during the period of organogenesis at doses up to approximately 50 and 200 times the MRHDID, respectively (on an AUC basis at maternal inhalation doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). No evidence of teratogenic effects was observed in either species.

In a perinatal and postnatal developmental study in rats, dams received umeclidinium during late gestation and lactation periods with no evidence of effects on offspring development at doses up to approximately 26 times the MRHDID (on an AUC basis at maternal subcutaneous doses up to 60 mcg/kg/day).

Vilanterol: In separate embryofetal developmental studies, pregnant rats and rabbits received vilanterol during the period of organogenesis at doses up to approximately 13,000 and 450 times, respectively, the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose in rats or in rabbits up to approximately 70 times the MRHDID (on an AUC basis at maternal doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

In a perinatal and postnatal developmental study in rats, dams received vilanterol during late gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in offspring development was observed.

8.2 Lactation

Risk Summary

There is no information available on the presence of umeclidinium or vilanterol in human milk, the effects on the breastfed child, or the effects on milk production. Umeclidinium was detected in the plasma of offspring of lactating rats treated with umeclidinium suggesting its presence in maternal milk. *(See Data.)* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANORO ELLIPTA and any potential adverse effects on the breastfed child from umeclidinium or vilanterol or from the underlying maternal condition.

Data

Subcutaneous administration of umeclidinium to lactating rats at ≥60 mcg/kg/day resulted in a quantifiable level of umeclidinium in 2 of 54 pups, which may indicate transfer of umeclidinium in milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 years and older and 478 subjects aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl <30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg of umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.2 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for the individual components, umeclidinium and vilanterol, as described below.

Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and at inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately equivalent to the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (both approximately 5,490 times the MRHDID based on AUC).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events

ANORO ELLIPTA is not indicated for the treatment of asthma. Inform patients that LABA, such as vilanterol (one of the active ingredients in ANORO ELLIPTA), when used alone (without ICS) for asthma increase the risk of asthma-related hospitalization or asthma-related death.

Not for Acute Symptoms

Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used. Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with ANORO ELLIPTA without healthcare provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm

As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA and contact their healthcare provider right away.

Risks Associated with Beta-agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Worsening of Narrow-Angle Glaucoma

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.

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Revised 7/2019 ANR:9BRS

UCVADVT190009 August 2019
Produced in USA.

Sleep problems can presage postnatal depression

BY BRUCE JANCIN
MDedge News

COPENHAGEN – Sleep problems during pregnancy are a risk factor for subsequent clinically significant postnatal depressive symptoms, Tiina Paunio, MD, PhD, reported at the annual congress of the European College of Neuropsychopharmacology.

"I think it is very important to understand that we need to screen pregnant women for sleep problems, even those without a history of depression, so we can have early treatment of insomnia – and also depression – because postnatal maternal depression is very much a risk for the child during a vulnerable period for development," said Dr. Paunio, professor of psychiatry at the University of Helsinki.

She was a coinvestigator in a prospective study of the Finnish CHILD-SLEEP longitudinal birth cohort in which 1,398 women completed the Basic Nordic Sleep Questionnaire and the 10-item version of the Center for Epidemiological Studies Depression Scale (CES-D) at about gestational week 32 and again around 3 months following delivery. Postnatal depressiveness as defined by a CES-D score of at least 10 points was present in 10.3% of the mothers. After adjusting for prenatal depressiveness and other potential confounders, the investigators found that tiredness during the day, poor general sleep quality, getting less than 6 hours of sleep, taking longer than 20 minutes to fall asleep, and sleep loss of 2 hours or more per night during pregnancy were each associated with clinically significant postnatal depressive symptoms, with odds ratios of 1.87-2.19.

BRUCE JANCIN/MDEDGE NEWS

Dr. Tiina Paunio

The full details of the study have been published (Arch Womens Ment Health. 2019 Jun;22[3]:327-37).

The impetus for this study of sleep problems in pregnancy as a predictor of postnatal depressive symptoms was a body of evidence linking insomnia to depression in both men and women. But it turns out that insomnia is a significant predictor of later onset of a wide variety of psychiatric disorders, not only depression, as highlighted in a recent systematic review and meta-analysis conducted by an international team of investigators, Dr. Paunio observed.

Baseline insomnia symptoms were associated with a 183% increased risk of later onset of depression, a 223% increased risk of anxiety, a 35% greater risk of alcohol abuse, and a 28% increased risk of psychosis. However, the insomnia/psychosis link must be viewed as tentative, as it was examined in only a single published study. The investigators rated the overall risk of bias in the studies included in their meta-analysis as moderate (Sleep Med Rev. 2019 Feb;43:96-105).

For Dr. Paunio, these findings suggest that interventional studies of early and effective treatment of insomnia as a potential means of preventing psychiatric disorders are in order.

She reported receiving research funding from the Academy of Finland, the Gyllenberg Foundation, and Finska Lakaresallskapet.

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Screen teens with insomnia for mental health disorders

BY JENNIE SMITH
MDedge News

Adolescents diagnosed with insomnia have a high prevalence of concurrent mental health disorders and should be screened for them, according to new research.

For a study published in the Journal of Clinical Sleep Medicine, Tori R. Van Dyk, PhD, of Loma Linda (Calif.) University, and colleagues, enrolled 376 adolescents aged 11-18 years (mean age 14.5, 55% female) diagnosed with primary insomnia and referred to a sleep clinic. Subjects were evaluated using two validated questionnaires used to measure sleep disorders in adolescents, while caregivers reported and mental health diagnoses and symptoms using a standard behavioral checklist for adolescents.

Dr. Van Dyk and colleagues found that 75% of subjects had at least one or more parent-reported mental health diagnosis, most commonly anxiety, mood disorders, and ADHD. Some 64% had a clinical elevation of mental health symptoms on evaluation, most commonly affective disorders, with 40% of the cohort having two or more elevations. Specific mental health symptoms were seen linked with particular sleep symptoms. A greater burden of ADHD symptoms, for example, was significantly associated with more difficulties falling asleep, maintaining sleep, and reinitiating sleep after waking at night.

A total of 15% of subjects were reported by caregivers to engage in deliberate self-harming behaviors or talking about or attempting suicide – a higher rate than in the general adolescent population. "Because youth presenting for insomnia treatment may be even more likely to engage in self-harm behavior or to be suicidal, particular attention should be paid to directly assessing for these high-risk behaviors within the context of behavioral sleep medicine evaluations," Dr. Van Dyk and colleagues wrote in their analysis.

Although mental health symptoms have been linked to sleep problems in other studies of children and adults, "associations identified in younger youths and/or adults should not be assumed to hold true among adolescents," the researchers wrote, adding that adolescence "is a distinctive developmental period characterized by increases in both psychopathology and sleep problems, changing biology, increasing independence, and unique social and societal demands." The investigators noted that because pediatric sleep specialists are relatively rare, the management of adolescent sleep problems and related mental health symptoms is likely to fall on primary care and other providers who "would benefit in recognizing the relationship between sleep problems and mental health symptoms in this population."

DEMAERRE/ISTOCK/GETTY IMAGES

Dr. Van Dyk and colleagues noted among the weaknesses of their study its cross-sectional design, use of parent-reported mental health symptoms only, lack of information on medication use or mental health treatment, and the potential for selection bias toward more severe cases.

The authors disclosed no outside funding or conflicts of interest related to their study.

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SOURCE: Van Dyk TR et al. J Clin Sleep Med. 2019 Sep 6. doi: 10.5664/jcsm.7970.

Dysregulated sleep is common in children with EoE

BY MICHELE G. SULLIVAN
MDedge News

Children with eosinophilic esophagitis (EoE) often experience respiratory and motor disturbances during sleep, which appear related to dysregulated sleep architecture, Rasintra Siriwat, MD, and colleagues have ascertained.

Children with EoE also were found to have a high prevalence of atopic diseases, including allergic rhinitis and eczema – findings that could be driving the breathing problems, said Dr. Siriwat, a neurology fellow at the Cleveland Clinic, and coauthors.

The retrospective study comprised 81 children with a diagnosis of EoE who were referred to sleep clinics. In this group, 46 of the children had active EoE (having gastrointestinal symptoms, including feeding difficulties, dysphagia, reflux, nausea/vomiting, or epigastric pain at presentation). The other 35 had an EoE diagnosis but no symptoms on presentation and were categorized as having inactive EoE. Most were male (71.6%) and white (92.5%). The mean age in the cohort was 10 years and the mean body mass index for all subjects was 22 kg/m^2. A control group of 192 children without an EoE diagnosis who had overnight polysomnography were included in the analysis.

Allergic-type comorbidities were common among those with active EoE, including allergic rhinitis (55.5%), food allergy (39.5%), and eczema (26%). In addition, a quarter had attention-deficit/hyperactivity disorder, 22% an autism spectrum disorder, 21% a neurological disease, and 29% a psychiatric disorder.

ALEX VASILEV/FOTOLIA

Several sleep complaints were common in the entire EoE cohort, including snoring (76.5 %), restless sleep (66.6%), legs jerking or leg discomfort (43.2%), and daytime sleepiness (58%).

All children underwent an overnight polysomnography. Compared with controls, the children with EoE had significantly higher non-REM2 sleep, significantly lower non-REM3 sleep, lower REM, increased periodic leg movement disorder, and increased arousal index.

"Of note, we found a much higher percentage of [periodic leg movement disorder] in active EoE compared to inactive EoE," the authors said.

The most common sleep diagnosis for the children with EoE was sleepd disordered breathing. Of 62 children with EoE and sleep disordered breathing, 37% had obstructive sleep apnea (OSA). Two patients had central sleep apnea and five had nocturnal hypoventilation. Children with EoE also reported parasomnia symptoms such as sleep talking (35.8%), sleepwalking (16%), bruxism (23.4%), night terrors (28.4%), and nocturnal enuresis (21.2%).

Of the 59 children with leg movement, 20 had periodic limb movement disorder and 5 were diagnosed with restless leg syndrome. Two were diagnosed with narcolepsy and three with hypersomnia. Four children had a circadian rhythm disorder.

"Notably, the majority of children with EoE had symptoms of sleep-disordered breathing, and more than one-third of total subjects were diagnosed with OSA," the authors noted. "However, most of them were mild-moderate OSA. It should be noted that the prevalence of OSA in the pediatric population is 1%-5% mostly between the ages of 2-8 years, while the mean age of our subjects was 10 years old. The high prevalence of mild-moderate OSA in the EoE population might be explained by the relationship between EoE and atopic disease."

Dr. Siriwat had no financial disclosures. The study was supported by Cincinnati Children's Hospital Research Fund.

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SOURCE: Siriwat R et al. Sleep Med. 2019 Sep 11. doi: 10.1016/j.sleep.2019.08.018.

Benzodiazepines, opioids carry greater risk of COPD-related hospitalization

BY JEFF CRAVEN
MDedge News

Patients with chronic obstructive pulmonary disease who received opioids or benzodiazepines had a greater risk of hospitalization for respiratory-related adverse events, according to recent research from Annals of the American Thoracic Society.

In addition, the risk of hospitalization because of respiratory events for patients with chronic obstructive pulmonary disease (COPD) was greater when opioid and benzodiazepine medications were combined, compared with patients who did not take either medication, Jacques G. Baillargeon, PhD, of the department of preventive medicine and community health at the University of Texas, Galveston, and colleagues wrote.

"Patients with COPD and their physicians should judiciously assess the risks and benefits of opioids and benzodiazepines, alone and in combination, and preferentially recommend nonopioid and nonbenzodiazepine approaches for pain, sleep, and anxiety management in patients with COPD," the investigators wrote.

The researchers performed a case-control study of 3,232 Medicare beneficiary cases of COPD patients who were aged at least 66 years. Patients were included if they experienced a hospitalization related to a COPD-related adverse event with a respiratory diagnosis in 2014 and then matched to one or two control patients (total, 6,247 patients) based on age at hospitalization, gender, COPD medication, COPD complexity, obstructive sleep apnea, and socioeconomic status. COPD complexity was assigned to three levels (low, moderate, high) and calculated using the patient's comorbid respiratory conditions and associated medical procedures in the 12 months prior to their hospitalization.

They found that, in the 30 days before COPD-related hospitalization, use of opioids was associated with greater likelihood of hospitalization (adjusted odds ratio, 1.73; 95% confidence interval, 1.52-1.97), as was use of benzodiazepines (aOR, 1.42; 95% CI, 1.21-1.66). When patients used both opioids and benzodiazepines, they had a significantly higher risk of hospitalization, compared with patients who did not use opioids or benzodiazepines (aOR, 2.32; 95% CI, 1.94-2.77).

In the 60 days prior to hospitalization, there was also a greater likelihood of hospitalization among COPD patients who used opioids (aOR, 1.66; 95% CI, 1.47-1.88), benzodiazepines (aOR, 1.44; 95% CI, 1.24-1.67), and both opioids and benzodiazepines (aOR, 2.27; 95% CI, 1.93-2.67); at 90 days, this higher risk of hospitalization persisted among COPD patients taking opioids (aOR, 1.58; 95% CI, 1.40-1.78), benzodiazepines (aOR, 1.40; 95% CI, 1.20-1.63), and both opioids and benzodiazepines (aOR, 2.21; 95% CI, 1.88-2.59).

The researchers acknowledged that one potential limitation in the study was how COPD diagnoses were obtained through coding performed by clinicians instead of from laboratory testing. Confounding by COPD indication and severity; use of over-the-counter medication or opioids and benzodiazepines received illegally; and lack of analyses of potential confounders such as diet, alcohol use, smoking status and herbal supplement use were other limitations.

This study was supported by an award from the National Center for Advancing Translational Sciences and National Institutes of Health. Dr. Baillargeon had no disclosures.

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SOURCE: Baillargeon JG et al. Ann Am Thorac Soc. 2019 Oct 1. doi: 10.1513/AnnalsATS.201901-024OC.

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TAVR, SAVR share same infective endocarditis risk

BY BRUCE JANCIN
MDedge News

PARIS – The risk of infective endocarditis following transcatheter aortic valve replacement (TAVR) for the treatment of severe aortic stenosis proved to be the same as after surgical replacement in a French national propensity score–matched study.

This finding from what is believed to be the largest-ever study of infective endocarditis following TAVR will come as a surprise to many physicians. It's easy to mistakenly assume the risk of this feared complication is lower – and perhaps even negligible – in TAVR patients since the procedure doesn't involve a significant surgical wound, it's briefer, the hospital length of stay is shorter, and recovery time is markedly less than with surgical aortic valve replacement (SAVR).

Not so, Laurent Fauchier, MD, PhD, said in presenting the study findings at the annual congress of the European Society of Cardiology.

"Do not think there is a lower risk of infective endocarditis. Be aware, be careful, and provide appropriate antibiotic prophylaxis, just as surgeons do in SAVR. Don't think, as I did, that with TAVR with no pacemaker implantation there is no risk of infective endocarditis. The TAVR valve is a device, it's a prosthesis, and the risk is very similar to that of surgery," advised Dr. Fauchier, a cardiologist at Francois Rabelais University in Tours, France.

He presented a study of all of the nearly 108,000 patients who underwent isolated TAVR or SAVR in France during 2010-2018. The data source was the French national administrative hospital discharge record system. Since the TAVR patients were overall markedly older and sicker than the SAVR patients, especially during the first years of the study, he and his coinvestigators performed propensity score matching using 30 variables, which enabled them to narrow the field of inquiry down to a carefully selected

Continued on following page

Bruce Jancin/MDedge News

Dr. Laurent Fauchier

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: Prosthetic valve endocarditis is a dreaded complication associated with a high mortality rate. This large study confirms that prosthetic valves are at risk for infection regardless of the technique used for the implantation. Anemia and atrial fibrillation as predictors of mortality in the TAVR group are hallmarks of higher comorbidity index. The study spans over 8 years and it is not clear whether the incidence rate of infection was different between the first half of the study vs the latter half. The message, however, is clear: meticulous surgical antisepsis and appropriate antibiotic prophylaxis should be used for TAVR patients similar to SAVR patients.

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These grants are supported by an independent educational grant from AstraZeneca LP.

Eric Abston, MD
CHEST Foundation Research Grant in Pulmonary Fibrosis

Karthik Suresh, MD
CHEST Foundation Research Grant in Pulmonary Fibrosis
These grants are supported by a scientific advancement agreement from Boehringer Ingelheim Pharmaceuticals, Inc and by a grant from Genentech.

Chris Mosher, MD
CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
This grant is supported in full by the CHEST Foundation.

Neelima Navuluri, MD, MPH
CHEST Foundation Research Grant in Women's Lung Health
This grant is supported in full by the CHEST Foundation.

Mitchell Cahan, MD
CHEST Foundation Research Grant in Venous Thromboembolism
This grant is supported in full by the CHEST Foundation.

Mona Alotaibi, MD
CHEST Foundation Research Grant in Pulmonary Arterial Hypertension
This grant is supported in full by the CHEST Foundation.

Kathleen Ramos, MD
CHEST Foundation Research Grant in Cystic Fibrosis
This grant is supported by Vertex Pharmaceuticals Incorporated.

Elsje Pienaar, PhD
CHEST Foundation Research Grant in Nontuberculosis Mycobacteria Diseases

Elisa Ignatius, MD
CHEST Foundation Research Grant in Nontuberculosis Mycobacteria Diseases
These grants are supported by Insmed Incorporated.

James Tsay, MD
CHEST Foundation Research Grant in Lung Cancer
This grant is supported in full by the CHEST Foundation.

Kamran Mahmood, MBBS, FCCP
The GlaxoSmithKline Distinguished Scholar in Respiratory Health
This grant is supported by an endowed fund from GlaxoSmithKline.

Derek Russel, MD
CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
This grant is supported by the Alpha-1 Foundation and the CHEST Foundation.

Divya Patel, DO
John R. Addrizzo, MD, FCCP, Research Grant in Sarcoidosis

Nicholas Arger, MD
John R. Addrizzo, MD, FCCP, Research Grant in Sarcoidosis
These grants are in honor of John R. Addrizzo, MD, FCCP, and are supported in full by the Addrizzo Family, their friends, and the CHEST Foundation.

Irene Telias, MD
CHEST Foundation Research Grant in Sleep Medicine

Sushmita Pamidi, MD, MSc
CHEST Foundation Research Grant in Sleep Medicine
These grants are supported by Apria Healthcare and Jazz Pharmaceuticals.

2019 COMMUNITY SERVICE GRANTEES

Each community service grantee received the CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP. This community service grant is supported in full by the CHEST Foundation.

Hans Lee, MD, FCCP
Panagis Galiatsatos, MD, MHS
Paul Sonenthal, MD
Dana Hickman, ARNP-C, FNP-BC
Ann Salvator, MS
Tisha Wang, MD

Beta-blockers safe for HFrEF with renal dysfunction

BY MITCHEL L. ZOLER
MDedge News

PARIS – Beta-blocking drugs were as effective for improving survival in patients with moderately severe renal dysfunction as they were in patients with normal renal function in a meta-analysis of more than 13,000 patients, a finding that seemed to solidify the role for this drug class for essentially all similar heart failure patients, regardless of their renal function.

This evidence could reshape usual care because "renal impairment is often considered a barrier in clinical practice" for starting a beta-blocker drug in patients with heart failure with reduced ejection fraction (HFrEF), Dipak Kotecha, MBChB, said at the annual congress of the European Society of Cardiology.

"We have shown with sufficient sample size that beta-blockers are effective in reducing mortality in patients with HFrEF and in sinus rhythm, even in those with an eGFR [estimated glomerular filtration rate] of 30-44 mL/min per 1.73 m^2," said Dr. Kotecha, a cardiologist at the University of Birmingham (England). "The results suggest that renal impairment should not obstruct the prescription and maintenance of beta-blockers in patients with HFrEF."

"This important study was a novel attempt to look at [HFrEF] patients with renal insufficiency to see whether they received the same benefit from beta-blockers as other patients, and they did. So renal insufficiency is not a reason to withhold beta-blockers" from these patients, commented Mariell Jessup, MD, a heart failure physician and chief science and medical officer for the American Heart Association in Dallas. "The onus is on clinicians to find a reason not to give a beta-blocker to a patient with HFrEF because they are generally well tolerated and they can have enormous benefit, as we saw in this study," she said in a video interview.


Dr. Kotecha

The analysis run by Dr. Kotecha and associates used data collected in 11 of the pivotal randomized, controlled trials run for beta-blockers during the 1990s and early 2000s, with each study comparing bucindolol, bisoprolol, carvedilol, metoprolol XL, or nebivolol against placebo. The studies collectively enrolled 18,637 patients, which the investigators whittled down in their analysis to 17,433 after excluding patients with a left ventricular ejection fraction below 50% or who were undocumented. The subgroup with HFrEF included 13,861 patients in sinus rhythm at entry, 2,879 with atrial fibrillation, and 693 with an unknown atrial status. The main analysis ran in the 13,861 patients with HFrEF and in sinus rhythm; 14% of this cohort had an eGFR of 30-44 mL/min per 1.73 m^2 and 27% had an eGFR of 45-59 mL/min per 1.73 m^2. The median age of all patients in the main analysis was 65 years, 23% were women, and their median left ventricular ejection fraction was 27%.

During follow-up of about 3 years, the impact of beta-blocker treatment on survival, compared with placebo, was "substantial" for all strata of patients by renal function, except for those with eGFRs below 30 mL/min per 1.73 m^2. (Survival was similar regardless of beta-blocker treatment in the small number of patients with severe renal dysfunction.) The number needed to treat to prevent one death in patients with an eGFR of 30-44 mL/min per 1.73 m^2 was 21, the same as among patients with an eGFR of 90 mL/min per 1.73 m^2 or more, Dr. Kotecha said.

Among the subgroup of patients with atrial fibrillation, beta-blockers appeared to exert no survival benefit, compared with placebo. The investigators did not assess the survival benefits exerted by any individual beta-blocker, compared with the others, and Dr. Kotecha stressed that "my belief is that this is a class effect" and is roughly similar across all the beta-blockers used in the studies.

The analysis also showed good safety and tolerability of the beta-blockers in patients with renal dysfunction. The incidence of adverse events leading to treatment termination was very similar in the beta-blocker and placebo arms, and more than three-quarters of patients in each of the two subgroups with renal dysfunction were maintained on more than 50% of their target beta-blocker dosage.

Dr. Kotecha has been an adviser to Bayer, has been a speaker on behalf of Atricure, and has received research funding from GlaxoSmithKline and Menarini. Dr. Jessup had no disclosures.

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Continued from previous page

study population of 16,291 TAVR patients and an equal number of closely similar SAVR patients.

A total of 1,070 cases of infective endocarditis occurred during a mean follow-up of just over 2 years. The rate of hospital admission for this complication was 1.89% per year in the TAVR group and similar at 1.71% per year in the SAVR cohort.

Of note, all-cause mortality in TAVR patients who developed infective endocarditis was 1.32-fold greater than it was in SAVR patients with infective endocarditis, a statistically significant difference. The explanation for the increased mortality risk in the TAVR group probably has to do at least in part with an inability on the part of the investigators to fully capture and control for the TAVR group's greater frailty, according to the cardiologist.

Risk factors for infective endocarditis shared in common by TAVR and SAVR patients included male gender, a higher Charlson Comorbidity Index score, and a greater frailty index. The main predictors unique to the TAVR patients were atrial fibrillation, anemia, and tricuspid regurgitation. And although pacemaker and defibrillator implantation were risk factors for infective endocarditis in the SAVR patients, it wasn't predictive of increased risk in the TAVR population. Dr. Fauchier called this finding "quite reassuring" given that roughly 20% of the TAVR group received a pacemaker.

The causative microorganisms for infective endocarditis were essentially the same in the TAVR and SAVR groups, simplifying antimicrobial prophylaxis decision making.

Dr. Fauchier reported having no financial conflicts regarding the study, conducted free of commercial support. He serves as a consultant to and/or on speakers' bureaus for Bayer, BMS Pfizer, Boehringer Ingelheim, Medtronic, and Novartis.

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European guidelines push LDL targets below 55 mg/dL

BY MITCHEL L. ZOLER
MDedge News

PARIS – The 2019 dyslipidemia management guidelines from the European Society of Cardiology set an LDL cholesterol target for very-high-risk people of less than 55 mg/dL (as well as at least a 50% cut from baseline), a class I recommendation. This marks the first time a cardiology society has either recommended a target goal for this measure below 70 mg/dL or endorsed treating patients to still-lower cholesterol once their level was already under 70 mg/dL.

The guidelines went further by suggesting consideration of an even lower treatment target for LDL cholesterol in very-high-risk, secondary-prevention patients who have already had at least two atherosclerotic cardiovascular disease events during the past 2 years, a setting that could justify an LDL cholesterol goal of less than 40 mg/dL (along with a cut from baseline of at least 50%), a class IIb recommendation that denotes a "may be considered" endorsement.

"In all the trials, lower was better. There was no lower level of LDL cholesterol that's been studied that was not better" for patient outcomes, Colin Baigent, BMBCH, said while presenting the new guideline at the annual congress of the European Society of Cardiology. "It's very clear" that the full treatment benefit from lowering LDL cholesterol extends to getting very-high-risk patients below these levels, said Dr. Baigent, professor of cardiology at Oxford (England) University and one of three chairs of the ESC's dyslipidemia guideline-writing panel.

While this change was seen as a notably aggressive goal and too fixed on a specific number by at least one author of the 2018 American Heart Association/American College of Cardiology cholesterol management guideline (J Am Coll Cardiol. 2019 Jun;73[24]:e285-350), it was embraced by another U.S. expert not involved in writing the most recent U.S. recommendations.

"A goal for LDL cholesterol of less than 55 mg/dL is reasonable; it's well documented" by trial evidence "and I support it," said Robert H. Eckel, MD, an endocrinologist and professor of medicine at the University of Colorado in Aurora. Dr. Eckel added that he "also supports" an LDL cholesterol of less than 40 mg/dL in very-high-risk patients with a history of multiple events or with multiple residual risk factors, and he said he has applied this lower LDL cholesterol goal in his practice for selected patients. But Dr. Eckel acknowledged in an interview that the evidence for it was less clear-cut than was the evidence behind a goal of less than 55 mg/dL. He also supported the concept of including a treatment goal in U.S. lipid recommendations, which in recent versions has been missing. "I fall back on a cholesterol goal for practical purposes" of making the success of cholesterol-lowering treatment easier to track.


Dr. Baigent


Dr. Stone


Dr. Sabatine

The new ESC goal was characterized as "arbitrary" by Neil J. Stone, MD, vice-chair of the panel that wrote the 2018 AHA/ACC guideline, which relied on treating secondary-prevention patients at high risk to an LDL cholesterol at least 50% less than before treatment, and recommended continued intensification for patients whose LDL cholesterol level remained at or above 70 mg/dL.

"If the patient is at 58 mg/dL, I'm not sure anyone can tell me what the difference is," compared with reaching less than 55 mg/dL, Dr. Stone said in an interview. "I worry about focusing on a number and not on the concept that people at the very highest risk deserve the most intensive treatment; the Europeans agree, but they have a different way of looking at it. Despite this difference in approach, the new ESC guidelines and the 2018 U.S. guideline "are more similar than different," stressed Dr. Stone, professor of medicine and preventive medicine at Northwestern University, Chicago.

However, other experts see an important difference in the risk faced by patients who reach the ESC's recommended treatment goals and those who fall just short.

"It's hard to lower an LDL cholesterol that is already relatively low. People who are close to their cholesterol target need the most intensified treatment" to reach their goal, said Rory Collins, FMedSci, professor of epidemiology at Oxford University. He was not on the ESC guidelines panel.

"It's a mind shift that clinicians need to be most aggressive in treating patients with the highest risk" even when their LDL cholesterol is low but not yet at the target level, Dr. Collins said during a discussion session at the congress.

The new ESC guidelines is about "both getting the LDL cholesterol down to a certain level and also about achieving a big [at least 50%] change" from baseline. "I think the ESC guidelines make that crystal clear," said Marc S. Sabatine, MD, professor of medicine at Harvard Medical School, Boston, and the sole American to participate in the ESC guidelines-writing panel.

The ESC also broke new ground by advocating an aggressive path toward achieving these LDL cholesterol goals by elevating the newest and most potent class of approved LDL cholesterol–lowering drugs, the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, to a top-tier, class I recommendation ("is recommended") for secondary prevention in very-high-risk patients not reaching their goal LDL cholesterol level on a maximally tolerated statin plus ezetimibe. This recommendation to unequivocally add a PCSK9 inhibitor for this patient population contrasts with the 2018 AHA/ACC guideline that deemed adding a PCSK9 inhibitor a IIa recommendation ("is reasonable").

A similar uptick in treatment aggressiveness appeared in the ESC's recommendations for managing very-high-risk patients in a primary prevention setting, including those without familial hypercholesterolemia. For these people, the ESC panel, which worked in concert with the European Atherosclerosis Society, pegged adding a PCSK9 inhibitor as a IIb ("may be considered") recommendation when these very-high-risk people fail to reach their LDL cholesterol target on a maximally tolerated statin and ezetimibe. Once again, this opening to use a PCSK9 inhibitor contrasted with the 2018 U.S. guideline, which never mentioned an option of adding a PCSK9 inhibitor for primary prevention except when someone also has familial hypercholesterolemia and starts treatment with an LDL level of at least 190 mg/dL (a IIb recommendation). The new European guidelines proposed using a PCSK9 inhibitor as a second-line option to consider when needed for people whose very high risk derives primarily from older age and other factors such as smoking or hypertension that give them at least a 10% 10-year risk for cardiovascular death as estimated with the European-oriented SCORE risk calculator tables.

Updated SCORE risk designations appear in the new ESC dyslipidemia guidelines, and they show, for example, that in lower-risk European countries (mostly Western European nations) virtually all men who are at least 70 years old would fall into the very-high-risk category that makes them potential candidates for treatment with a PCSK9 inhibitor regardless of any other risk they may or may not have. In higher-risk (mostly Eastern European) countries this designation kicks in for most men once they reach the age of 65.

Several Congress attendees who came to a discussion session on the guidelines voiced concerns that the new revision will lead to substantially increased use of the these drugs and hence will significantly boost medical costs, because these drugs today are priced at about $6,000 annually to treat one patient. In response, members of the guideline-writing panel defended their decision as unavoidable given what's been reported on the clinical impact of PCSK9 inhibitors when lowering LDL cholesterol and cutting atherosclerotic cardiovascular disease events.

Dr. Baigent has received research funding from Boehringer Ingelheim, Novartis, and Pfizer. Dr. Eckel has been an expert witness on behalf of Sanofi/Regeneron. Dr. Sabatine and Dr. Ference have received honoraria and research funding from several companies including those that market lipid-lowering drugs. Dr. Stone and Dr. Collins had no disclosures.

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SOURCE: Mach F et al. Eur Heart J. 2019 Aug 31. doi: 10.1093/eurheartj/ehz455.

ONCE-DAILY
YUPELRI®
revefenacin inhalation solution
Relief that matters

The FIRST AND ONLY once-daily nebulized LAMA, for a full 24 hours of lung function improvement[1]

Proven 24-hour control[1]
Consistent improvement in trough FEV_1 vs placebo over 24 hours on days 84/85[1,2]

The primary endpoint was change from baseline in trough (predose) FEV_1 at day 85 vs placebo: YUPELRI demonstrated a statistically significant difference vs placebo in study 1 (146 mL, *P*<.0001 [YUPELRI, n=189; placebo, n=191]) and study 2 (147 mL, *P*<.0001 [YUPELRI, n=181; placebo, n=187]).[1,2]

In study 1, LS mean changes from baseline in FEV_1 ranged from 55.8 mL to 240.4 mL in the YUPELRI group, and from -113.6 mL to 59.6 mL in the placebo group. In study 2, LS mean changes from baseline in FEV_1 ranged from 19.8 mL to 148.5 mL in the YUPELRI group, and from -176.4 mL to -13.0 mL in the placebo group.

In studies 1 and 2, a prespecified exploratory analysis using serial spirometry was performed on a substudy population (YUPELRI, n=89; placebo, n=83) over 24 hours on days 84/85. In a pooled analysis, YUPELRI demonstrated consistent improvement in trough FEV_1 vs placebo over the 24-hour period.

Demonstrated safety profile[1]
Refer to the Important Safety Information below for additional information

Once-daily dosing[1]
Administered with any standard jet nebulizer with a mouthpiece

Up to 100% of patients with Medicare Part B are expected to be covered*
Permanent J-CODE J7677

*This is not a guarantee of coverage. Site of care will determine coverage. Check with your patient's insurance provider for coverage rules and restrictions. In certain limited instances, YUPELRI may be covered through a patient's Medicare Part D pharmacy benefit.

Indication

YUPELRI® inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Important Safety Information

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

YUPELRI should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD, or for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist.

As with other inhaled medicines, YUPELRI can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing with YUPELRI, it should be treated immediately with an inhaled, short-acting bronchodilator. YUPELRI should be discontinued immediately and alternative therapy should be instituted.

YUPELRI should be used with caution in patients with narrow-angle glaucoma. Patients should be instructed to immediately consult their healthcare provider if they develop any signs and symptoms of acute narrow-angle glaucoma, including eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema.

Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur.

Immediate hypersensitivity reactions may occur after administration of YUPELRI. If a reaction occurs, YUPELRI should be stopped at once and alternative treatments considered.

The most common adverse reactions occurring in clinical trials at an incidence greater than or equal to 2% in the YUPELRI group, and higher than placebo, included cough, nasopharyngitis, upper respiratory infection, headache and back pain.

Coadministration of anticholinergic medicines or OATP1B1 and OATP1B3 inhibitors with YUPELRI is not recommended.

YUPELRI is not recommended in patients with any degree of hepatic impairment.

Please see Brief Summary of Full Prescribing Information on the adjacent pages.

Learn more at YUPELRIHCP.com

References: 1. YUPELRI [package insert]. Morgantown, WV: Mylan Specialty L.P.; May 2019. **2.** Data on file.

Mylan® Theravance Biopharma

YUPELRI® (revefenacin) inhalation solution, for oral inhalation

Initial U.S. Approval: 2018

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

YUPELRI inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

WARNINGS AND PRECAUTIONS

Deterioration of Disease and Acute Episodes

YUPELRI should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD. YUPELRI has not been studied in subjects with acutely deteriorating COPD. The initiation of YUPELRI in this setting is not appropriate.

YUPELRI is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If YUPELRI no longer controls symptoms of bronchoconstriction, the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of a short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of YUPELRI beyond the recommended dose is not appropriate in this situation.

Paradoxical Bronchospasm

As with other inhaled medicines, YUPELRI can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing with YUPELRI, it should be treated immediately with an inhaled, short-acting bronchodilator; YUPELRI should be discontinued immediately and alternative therapy should be instituted.

Worsening of Narrow-Angle Glaucoma

YUPELRI should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention

YUPELRI should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g. difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of YUPELRI. If such a reaction occurs, therapy with YUPELRI should be stopped at once and alternative treatments should be considered.

ADVERSE REACTIONS

The following potential adverse reactions are described in greater detail in other sections:

- Paradoxical bronchospasm *[see Warnings and Precautions]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions]*
- Worsening of urinary retention *[see Warnings and Precautions]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions]*

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The YUPELRI safety database included 2,285 subjects with COPD in two 12-week efficacy studies and one 52-week long-term safety study. A total of 730 subjects received treatment with YUPELRI 175 mcg once daily. The safety data described below are based on the two 12-week trials and the one 52-week trial.

12-Week Trials

YUPELRI was studied in two 12-week replicate placebo-controlled trials in patients with moderate to very severe COPD (Trials 1 and 2). In these trials, 395 patients were treated with YUPELRI at the recommended dose of 175 mcg once daily.

The population had a mean age of 64 years (range from 41 to 88 years), with 50% males, 90% Caucasian, and had COPD with a mean post-bronchodilator forced expiratory volume in one second (FEV_1) percent predicted of 55%. Of subjects enrolled in the two 12-week trials, 37% were taking concurrent LABA or ICS/LABA therapy. Patients with unstable cardiac disease, narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

Table 1 shows the most common adverse reactions that occurred with a frequency of greater than or equal to 2% in the YUPELRI group and higher than placebo in the two 12 week placebo- controlled trials.

The proportion of subjects who discontinued treatment due to adverse reactions was 13% for the YUPELRI-treated subjects and 19% for placebo-treated subjects.

Table 1: Adverse Events with YUPELRI ≥2% Incidence and Higher than Placebo

	Placebo (N = 418)	YUPELRI 175 mcg (N = 395)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17 (4%)	17 (4%)
Infections and Infestations		
Nasopharyngitis	9 (2%)	15 (4%)
Upper respiratory tract infection	9 (2%)	11 (3%)
Nervous System Disorders		
Headache	11 (3%)	16 (4%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	3 (1%)	9 (2%)

Other adverse reactions defined as events with an incidence of ≥1.0%, less than 2.0%, and more common than with placebo included the following: hypertension, dizziness, oropharyngeal pain, and bronchitis.

52-Week Trial

YUPELRI was studied in one 52-week, open-label, active-control (tiotropium 18 mcg once daily) trial in 1,055 patients with COPD. In this trial, 335 patients were treated with YUPELRI 175 mcg once daily and 356 patients with tiotropium. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled 12-week studies described, with the exception that concurrent LABA or LABA/ICS therapy was used in 50% of patients. The adverse reactions reported in the long-term safety trial for YUPELRI were consistent with those observed in the placebo-controlled studies of 12-weeks.

DRUG INTERACTIONS

Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of YUPELRI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions]*.

Transporter-Related Drug Interactions

OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.) could lead to an increase in systemic exposure of the active metabolite. Therefore, coadministration with YUPELRI is not recommended *[see Clinical Pharmacology.]*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with YUPELRI in pregnant women. Women should be advised to contact their physician if they become pregnant while taking YUPELRI. In animal reproduction studies, subcutaneous administration of revefenacin to pregnant rats and rabbits during the period of organogenesis produced no evidence of fetal harm at respective exposures approximately 209 times the exposure at the maximum recommended human dose (MRHD) (on an area under the curve [AUC] basis) *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 17, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 209 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

In an embryo fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7 to 19, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 694 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Placental transfer of revefenacin and its active metabolite was observed in pregnant rabbits.

In a pre- and postnatal development (PPND) study in pregnant rats dosed during the periods of organogenesis and lactation from gestation day 6 to lactation day 20, revefenacin had no adverse developmental effects on pups at exposures up to 196 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Lactation

Risk Summary

There is no information regarding the presence of revefenacin in human milk, the effects on the breastfed infant, or the effects on milk production. However, revefenacin was present in the milk of lactating rats following dosing during pregnancy and lactation *(see Data).*

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YUPELRI and any potential adverse effects on the breastfed infant from YUPELRI or from the underlying maternal condition.

Data

Animal Data

In a PPND study *[see Pregnancy],* revefenacin and its active metabolite were present in milk of lactating rats on lactation day 22. Milk-to-plasma concentration ratios were up to 10 for revefenacin and its active metabolite.

Pediatric Use

YUPELRI is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

Geriatric Use

Based on available data, no adjustment of the dosage of YUPELRI in geriatric patients is necessary.

Clinical trials of YUPELRI included 441 subjects aged 65 years and older, and of those, 101 subjects were aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

The systemic exposure of revefenacin is unchanged while that of its active metabolite is increased in subjects with moderate hepatic impairment. The safety of YUPELRI has not been evaluated in COPD patients with mild-to-severe hepatic impairment. YUPELRI is not recommended in patients with any degree of hepatic impairment. *[see Clinical Pharmacology].*

Renal Impairment

No dosage adjustment is required in patients with renal impairment. Monitor for systemic antimuscarinic side effects in COPD patients with severe renal impairment. *[see Clinical Pharmacology].*

OVERDOSAGE

An overdose of YUPELRI may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation or difficulties in voiding. In COPD patients, orally inhaled administration of YUPELRI at a once-daily dose of up to 700 mcg (4 times the maximum recommended daily dose) for 7 days was well tolerated.

Treatment of overdosage consists of discontinuation of YUPELRI along with institution of appropriate symptomatic and/or supportive therapy.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year inhalation studies in Sprague-Dawley rats and CD1 mice were conducted to assess the carcinogenic potential of revefenacin. No evidence of tumorigenicity was observed in male and female rats at inhaled doses up to 338 mcg/kg/day (approximately 35 times the MRHD based upon summed AUCs for revefenacin and its active metabolite). No evidence of tumorigenicity was observed in male and female mice at inhaled doses up to 326 mcg/kg/day (approximately 40 times the MRHD based on summed AUCs for revefenacin and its active metabolite).

Revefenacin and its active metabolite were negative for mutagenicity in the Ames test for bacterial gene mutation. Revefenacin was negative for genotoxicity in the *in vitro* mouse lymphoma assay and *in vivo* rat bone marrow micronucleus assay.

There were no effects on male or female fertility and reproductive performance in rats at subcutaneous revefenacin doses up to 500 mcg/kg/day (approximately 30 times the MRHD on an mg/m^2 basis for revefenacin).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use) with each new prescription and refill.

Not for Acute Symptoms

Inform patients that YUPELRI is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with YUPELRI without healthcare provider guidance since symptoms may recur after discontinuation.

Paradoxical Bronchospasm

As with other inhaled medicines, YUPELRI can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue YUPELRI.

Worsening of Narrow-Angle Glaucoma

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g. difficulty passing urine, painful urination). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Instructions for Administering YUPELRI

It is important for patients to understand how to correctly administer YUPELRI using a standard jet nebulizer [see Instructions for Use]. Instruct patients that YUPELRI should only be administered via a standard jet nebulizer. Patients should be instructed not to inject or swallow the YUPELRI solution. Patients should be instructed not to mix other medications with YUPELRI.

Patients should not inhale more than one dose at any one time. The daily dosage of YUPELRI should not exceed one unit-dose vial. Inform patients to use the contents of one vial of YUPELRI orally inhaled daily at the same time every day. Patients should throw the plastic dispensing vials away immediately after use. Due to their small size, the vials pose a danger of choking to young children.

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Next-generation genomic test plus bronchoscopy may improve lung nodule management

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – The use of a next-generation genomic test may enable improved management of patients with pulmonary nodules when results of bronchoscopy are inconclusive, results of a recent clinical validation study suggest.

The Percepta Genomic Sequencing Classifier (GSC) was able to up- and down-classify probability of malignancy for a considerable proportion of nondiagnostic bronchoscopies in the study, Peter J. Mazzone MD, FCCP, reported at the annual meeting of the American College of Chest Physicians.

The test is seen as complementary to bronchoscopy, improving the sensitivity of bronchoscopy overall and showing a combined sensitivity of greater than 95% in low- and intermediate-risk groups, according to Dr. Mazzone.

While the clinical utility of this genomic test needs to be further tested, the eventual goal is to improve clinician decision making when bronchoscopy results don't clearly classify nodules as malignant or benign, Dr. Mazzone said in an interview.

"In that situation, you're often left wondering, 'what should I do next? Can I just watch this, and see if it grows and changes, or do I have to be even more aggressive – do another biopsy, or have a surgery to take it out?'" he explained. "So the test hopes to help make a more informed decision by further stratifying those patients as being quite low risk and maybe safe to follow, or quite high risk and maybe you should be considering more aggressive management."

The GSC improves on the performance of an earlier molecular test, the Percepta Bronchial Genomic Classifier, which uses a brushing of bronchial epithelium to enhance nodule management in smokers, according to the researcher.

The next-generation GSC uses 1,232 gene transcripts from whole-transcriptome RNA sequencing, along with clinical factors, to help with nodule diagnosis, he said.

To establish the diagnostic accuracy of the GSC, Dr. Mazzone and colleagues evaluated data on 412 patients from three independent cohorts, all of whom had bronchoscopies for lung nodule evaluation that were nondiagnostic. Of those patients, 5% had nodules that physicians had deemed as low probability of malignancy prior to bronchoscopy, 28% deemed intermediate risk, and 74% high risk.

They found that the Percepta GSC down-classified the low–pretest risk patients with 100% negative predictive value (NPV) and down-classified intermediate–pretest risk patients with a 91.0% NPV, Dr. Mazzone reported, while patients with intermediate pretest risk were up-classified with a 65.4% positive predictive value (PPV) and patients with high pretest risk were upclassified with a 91.5% PPV.

The proportion of patients reclassified was about 55% for the low-risk group, 42% for the intermediate-risk group, and 27% for the high-risk group, according to the report at the meeting.

These results suggest the Percepta GSC could help in the "sticky situation" where a bronchoscopy result is inconclusive, Dr. Mazzone told attendees.

"When a bronchoscopy is recommended, despite fantastic advances in navigation systems to get to those nodules, we often come back without a solid answer, and that leaves the clinician in a bit of a predicament," he said in a late-breaking clinical trial presentation.

Dr. Mazzone provided disclosures related to Veracyte, Exact Sciences, SEER, Tencent, and PCORI (research support to institution).

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SOURCE: Mazzone PJ et al. CHEST 2019, Abstract. doi: 10.1016/j.chest.2019.08.307.

Survey finds barriers to molecular testing for lung cancer

BY SHARON WORCESTER
MDedge News

BARCELONA – Molecular testing to guide treatment in patients with lung cancer remains underused, and awareness of related evidence-based guidelines is suboptimal, results of an international survey suggest.

Overall, 61% of the 2,537 respondents from 102 countries and across multiple relevant medical specialties reported that molecular testing rates in their country were less than 50%, with the lowest rates reported in Latin America. And 33% of those requesting molecular testing said they were unaware of the most updated guidelines supporting the use of such testing in lung cancer, Matthew Smeltzer, PhD, of the University of Memphis reported during a press conference at the World Conference on Lung Cancer.

The findings from the International Association for the Study of Lung Cancer Global Survey on Molecular Testing in Lung Cancer also showed that 41% of respondents who perform or interpret molecular testing assays report being dissatisfied with the conditions of molecular testing in their country, 17% said they feel that patients are not satisfied, and 35% said they aren't sure about the state of testing in their country.

Specific concerns reported by respondents included trouble understanding results, the time it takes to receive the results, and the reliability of samples.


Sharon Worcester/MDedge News

Dr. Matthew Smeltzer

The top five barriers to molecular testing included cost, quality, access, awareness, and time, Dr. Smeltzer said at the meeting which is sponsored by the IASLC.

"These five were the same five top barriers in each region of the world," he said, noting that the ordering of the barriers differed somewhat among regions.

The survey included a 7-question introduction, with 32 additional questions for respondents who request tests and treat patients, 45 questions on performing and interpreting assays, and 24 questions on tissue acquisition. Additionally, all respondents were asked to list barriers that impede their country's ability to offer molecular testing.

"I'd say we got a pretty good geographic distribution of responses; 56% of these responses were from developing countries, 44% from developed countries," he said, noting that medical oncologists constituted the highest percentage of respondents, followed by pulmonologists, thoracic surgeons, pathologists, and other scientists.

When asked specifically what would prompt molecular testing, respondents most often listed adenocarcinoma, never-smoker status, female gender, and young age, Dr. Smeltzer said.

"Overall, we're still finding that many in the lung cancer community are not satisfied with the current state of molecular testing. We've got suboptimal awareness of the evidence-based guidelines. We have barriers that remain to molecular testing, which we've identified, and [we're] recommending continuous education around molecular testing, and that should be intensified on a national and international level to ensure that patients receive optimal therapy," he concluded.

The IASLC survey was funded by AstraZeneca. Dr. Smeltzer reported receiving research support from the Bristol Myers Squibb Foundation.

sworcester@mdedge.com

INDICATION

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

LIMITATION OF USE

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Eosinophilic Conditions: Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA), conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with EGPA have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the chronic rhinosinusitis with nasal polyposis development program. A causal association between DUPIXENT and these conditions has not been established.

Acute Asthma Symptoms or Deteriorating Disease: Do not use DUPIXENT to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of DUPIXENT.

LEARN MORE AT *DUPIXENTASTHMAHCP.COM*

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **81%**

REDUCTION IN ANNUALIZED RATE OF SEVERE EXACERBATIONS through Week 24[1,b]

- **71% REDUCTION** with DUPIXENT 200 mg + SOC (n=65) vs placebo + SOC (n=68) (0.30 vs 1.04; rate ratio: 0.29 [95% CI: 0.11, 0.76])
- **81% REDUCTION** with DUPIXENT 300 mg + SOC (n=64) vs placebo + SOC (n=68) (0.20 vs 1.04; rate ratio: 0.19 [95% CI: 0.07, 0.56])

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **430 mL**

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12[1]

- **430 mL IMPROVEMENT** with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL])
- **390 mL IMPROVEMENT** with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL])

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

TRIAL 1: 24-WEEK STUDY–776 adults (≥18 years) with moderate-to-severe asthma on a standard of care of medium- or high-dose ICS and a LABA were randomized to either DUPIXENT 200 mg Q2W[c] + SOC (n=150), DUPIXENT 300 mg Q2W[d] + SOC (n=157), or placebo + SOC (n=158). Subjects enrolled in Trial 1 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. DUPIXENT was administered as an add-on to background asthma treatment. **Primary endpoint:** Mean change from baseline to Week 12 in FEV_1 in patients with baseline eosinophils ≥300 cells/µL. **Other endpoint:** Annualized rate of severe exacerbation events during the 24-week treatment period.[e] **Selected baseline demographics:** Mean duration of asthma: 22 years; mean exacerbations in previous year: 2.2; high-dose ICS use: 50%; pre-dose FEV_1 at baseline: 1.84 L; mean FeNO: 39 ppb; mean total IgE: 435 IU/mL; and mean baseline blood eosinophil count: 350 cells/µL.

[b] Severe exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
[c] With 400 mg loading dose.
[d] With 600 mg loading dose.
[e] Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LSM, least squares mean; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

Please see additional Important Safety Information throughout and brief summary of full Prescribing Information on the following pages.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION WITH DUPIXENT[1]

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

↑ 430 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL]) and sustained through 24 weeks (380 mL vs 220 mL)

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

↑ 390 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL]) and sustained through 24 weeks (380 mL vs 220 mL)

~68% OF THE TOTAL IMPROVEMENT IN FEV_1 SEEN AT WEEK 2 WITH DUPIXENT 200 mg + SOC (Trial 1 ≥300 cells/µL)[2]

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥1%) in patients with asthma are injection site reactions, oropharyngeal pain, and eosinophilia.

DRUG INTERACTIONS: Avoid use of live vaccines in patients treated with DUPIXENT.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

MORE PATIENTS STOPPED USING OCS WITH DUPIXENT WHILE IMPROVING ASTHMA CONTROL[1,3]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

70%

REDUCTION IN OCS DOSE

(median 100%) from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) (95% CI: 60%, 80%) vs **42%** (median 50%) with placebo + SOC (n=107)

86% OF PATIENTS REDUCED OR ELIMINATED THEIR OCS DOSE with DUPIXENT 300 mg + SOC (n=103) vs **68%** with placebo + SOC (n=107)

IMPROVE LUNG FUNCTION AND REDUCE SEVERE EXACERBATIONS WITH THE ONLY BIOLOGIC INDICATED FOR OCS-DEPENDENT ASTHMA PATIENTS, REGARDLESS OF PHENOTYPE[b]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

59%
REDUCTION

IN ANNUALIZED RATE OF SEVERE EXACERBATIONS
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs placebo + SOC (n=107) (0.65 vs 1.60; rate ratio: 0.41 [95% CI: 0.26, 0.63])

220 mL
IMPROVEMENT

IN PRE-BRONCHODILATOR FEV_1
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs **10 mL** with placebo + SOC (n=107) (LSM difference: 220 mL [95% CI: 90, 340 mL])

TRIAL 3: 24-WEEK STUDY–210 subjects (≥12 years) with asthma who required daily OCS in addition to regular use of standard of care of high-dose ICS plus an additional controller medication were randomized to either DUPIXENT 300 mg Q2W[c] + SOC + OCS (n=103) or placebo + SOC + OCS (n=107); the baseline mean OCS dose was 11 mg in the DUPIXENT group and 12 mg in the placebo group. **Primary endpoint:** Percent reduction from baseline in OCS dose at Week 24, while maintaining asthma control, in the overall population. **Additional secondary endpoints:** Annualized rate of severe exacerbation events during the 24-week treatment period; and mean change from baseline to Week 24 in FEV_1. **Selected baseline demographics:** Mean duration of asthma: 20 years; mean exacerbations in previous year: 2.1; high-dose ICS use: 89%; pre-dose FEV_1 at baseline: 1.58 L; mean FeNO: 38 ppb; mean total IgE: 431 IU/mL; and mean baseline blood eosinophil count: 350 cells/μL.

[a] Intention-to-treat (ITT) population was unrestricted by minimum baseline eosinophils or other Type 2 biomarkers (eg, FeNO or IgE).
[b] Asthma exacerbation was defined as a temporary increase in OCS dose for at least 3 days.
[c] With 600 mg loading dose.

Please see brief summary of full Prescribing Information on the following pages.

References: 1. DUPIXENT Prescribing Information. **2.** Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. **3.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485.

SANOFI GENZYME

REGENERON

DUP.19.08.0282

DUPIXENT® (dupilumab) injection, for subcutaneous use Rx Only
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis *[see Adverse Reactions (6.2)]*. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program, as well as in adult patients with comorbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPIXENT should not be used to treat acute asthma symptoms or acute exacerbations. Do not use DUPIXENT to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT.

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 3: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*.

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions:

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular (CV)

In the 1-year placebo-controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, nonfatal myocardial infarctions [MI], and nonfatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described that follow, with the incidence of antibodies in other studies or to other products, may be misleading. Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had

neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.

Please call 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level, which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.5)]*.

Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 U.S. License # 1760; Marketed by sanofi-aventis U.S. LLC, (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591) /DUPIXENT is a registered trademark of Sanofi Biotechnology/Issue Date: August 2019 DUP.19.08.0026

LDCT plus miRNA bolsters prevention efforts

BY SHARON WORCESTER
MDedge News

BARCELONA – Adding a blood microRNA (miRNA) assay to low-dose computed tomography (LDCT)–based lung cancer screening in heavy smokers bolsters lung cancer prevention efforts, according to findings from the prospective bioMILD trial.

Specifically, the addition of the miRNA assay appears to reduce unnecessary repeat LDCT scans based on individual risk profiles without adversely affecting lung cancer detection or mortality, Ugo Pastorino, MD, director of thoracic surgery at the Istituto Nazionale dei Tumori Foundation, Milan, reported at the World Conference on Lung Cancer.

Of 4,119 volunteers with a median age of 60 years and a median of 42 pack-years who were enrolled between January 2013 and March 2016, 2,384 (58%) were assigned a 3-year LDCT repeat according to their double-negative baseline LDCT and miRNA profile, whereas 1,526 (37%) with a single-positive screen (either a positive miRNA or indeterminate/positive LDCT) and 209 (5%) with double positive (both a positive miRNA and indeterminate/positive LDCT) were assigned to annual or shorter LDCT repeat.

After four screening runs, a total of 115 lung cancers were diagnosed. The cumulative lung cancer rates "were enormously different" in the 3 groups, despite similar group composition with respect to age, gender, and tobacco consumption (0.6% for double-negative screening, 3.8% for single-positive screening, and 20.1% for double -positive screening), and lung cancer mortality was 0.1%, 0.6%, and 3.8% in the groups, respectively, Dr. Pastorino said at the conference, which is sponsored by the International Association for the Study of Lung Cancer.

However, no significant differences were seen in the proportion of stage I lung cancers, resection rates, or interval cancer incidence in subjects sent to 3-year LDCT repeat, he noted.

Sharon Worcester/MDedge News

Dr. Ugo Pastorino

The bioMILD trial was designed in the wake of the National Lung Screening Trial (NLST), which showed that three annual LDCT rounds for lung cancer screening reduced lung cancer mortality, and the Multicentric Italian Lung Detection (MILD) trial, which provided additional evidence that intervention beyond 5 years with annual or biennial rounds enhanced the benefit of screening.

Dr. Pastorino, the lead author on the MILD trial, previously reported that miRNA expression profiles in tumors and in normal lung tissue indicate aggressive lung cancer development and that specific miRNA signatures can be identified in plasma samples up to 2 years before spiral-CT detection of the disease.

The bioMILD trial tested the additional value of an miRNA assay at the time of LDCT.

Subjects were current (79%) or former heavy smokers, and 39% were women.

The findings suggest that adding the miRNA assay to LDCT for lung cancer screening is a "valuable and safe tool to assess individual risk profile and reduce unnecessary LDCT repeats in lung cancer screening," Dr. Pastorino said.

"But what is more important for us [is that] the knowledge of individual biologic risk can improve the efficacy of screening, but can [also] guide prevention strategies because the problem in a heavy smoker is not to just detect lung cancer, it's to reduce mortality," he said at a press conference highlighting the findings. "And so, personalized prevention is a real option now, and that means diagnosis, but also preventive measures [such as] smoking cessation and chemoprevention."

Invited discussant Harry J. de Koning, MD, PhD, professor of public health and screening evaluation at Erasmus Medical Center, Rotterdam, the Netherlands, noted that no other studies have evaluated screening intervals longer than 2 years, but he agreed that "reducing regular follow-up scans based on additional risk information is a way forward."

However, the approach would increase costs, he said, adding that large, prospective, randomized, controlled trials are needed to confirm the safety of such approaches in nationwide programs.

Dr. Pastorino and Dr. de Koning each reported having no disclosures.

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SOURCE: Pastorino U et al. WCLC 2019, Abstract PL02.04

Cardiotoxicity after checkpoint inhibitor treatment seen early, linked to elevated biomarkers

BY ANDREW D. BOWSER
MDedge News

PHILADELPHIA – While immune checkpoint inhibitors were not significantly more cardiotoxic than other lung cancer treatments, major adverse cardiac events (MACE) did occur earlier, and occurred more frequently in patients with elevated biomarkers, in a retrospective cohort study reported at the annual scientific meeting of the Heart Failure Society of America.

The findings support monitoring of cardiac biomarkers in the initial phase of checkpoint inhibitor treatment to identify patients at high cardiac risk, according to Kalyan R. Chitturi, DO, a resident physician with the DeBakey Heart and Vascular Center, Houston Methodist Hospital, who presented the results.

"It's the early period that warrants the closest monitoring, as within the first 30-40 days, there's higher risk," Dr. Chitturi said in an interview. "When there was a biomarker elevation, it markedly increased the risk of MACE, warranting a closer vigilance during that time period."

The retrospective study conducted by Dr. Chitturi and colleagues included a total of 252 patients with lung cancer who had been treated at one of seven different sites in Houston Methodist Cancer Center between Aug. 1, 2015, and Aug. 1, 2018.

Immune checkpoint inhibitors did not significantly increase the risk of MACE, compared with other lung cancer therapies, with incidences of 13.3% and 10.3%, respectively (P = .632), the investigators found.

However, MACE did occur earlier in the checkpoint inhibitor group, at a median time to event of 40 days, compared with 118 days in the patients not treated with checkpoint inhibitors, they found.

Risk of MACE with checkpoint inhibitor treatment was increased in patients with elevated troponin (hazard ratio, 2.48; 95% confidence interval, 1.18-5.21; P = .017) or elevated brain natriuretic peptide (HR, 5.77; 95% CI, 2.70-12.35; P less than .001), according to multivariate logistic regression analysis results.

These results suggest biomarkers such as cardiac troponin and brain natriuretic peptide are warranted to monitor patients in the early phase of checkpoint inhibitor treatment, according to Dr. Chitturi. "In the cost-benefit ratio of often-lethal MACE, it's well worth it to collect these," he said in the interview.

The results corroborate findings from some other recent studies, he noted. These include a recent study that linked elevated serum troponin to myocarditis in patients treated with immune checkpoint inhibitors (J Am Coll Cardiol. 2018 Apr 24;71[16]:1755-64).

Dr. Chitturi and coauthors reported no disclosures related to their presentation at the HFSA meeting.

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SOURCE: Chitturi KR et al. HFSA 2019, Abstract 127.

Vitamin C–based regimens in sepsis plausible, need more data, expert says

BY ANDREW D. BOWSER
MDedge News

EXPERT ANALYSIS FROM CHEST 2019 ▪ While further data are awaited on the role of vitamin C, thiamine, and steroids in sepsis, there is at least biologic plausibility for using the combination, and clinical equipoise that supports continued enrollment of patients in the ongoing randomized, controlled VICTAS trial, according to that study's principal investigator.

"There is tremendous biologic plausibility for giving vitamin C in sepsis," said Jon Sevransky, MD, professor of medicine at Emory University in Atlanta. But until more data are available on vitamin C–based regimens, those who choose to use vitamin C with thiamine and steroids in this setting need to ensure that glucose is being measured appropriately, he warned.

Andrew Bowser/MDedge News

Dr. Jon Sevransky

"If you decide that vitamin C is right for your patient, prior to having enough data – so if you're doing a Hail Mary, or a 'this patient is sick, and it's probably not going to hurt them' – please make sure that you measure your glucose with something that uses whole blood, which is either a blood gas or sending it down to the core lab, because otherwise, you might get an inaccurate result," Dr. Sevransky said at the annual meeting of the American College of Chest Physicians.

Results from the randomized, placebo-controlled Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS) trial may be available within the next few months, according to Dr. Sevransky, who noted that the trial was funded for 500 patients, which provides an 80% probability of showing an absolute risk reduction of 10% in mortality.

The primary endpoint of the phase 3 trial is vasopressor- and ventilator-free days at 30 days after randomization, while 30-day mortality has been described as "the key secondary outcome" by Dr. Sevransky and colleagues in a recent report on the trial design.

Clinicians have been "captivated" by the potential benefit of vitamin C, thiamine, and hydrocortisone in patients with severe sepsis and septic shock, as published in CHEST in June 2017, Dr. Sevransky said. In that study, reported by Paul E. Marik, MD, and colleagues, hospital mortality was 8.5% for the treatment group, versus 40.4% in the control group, a significant difference.

That retrospective, single-center study had a number of limitations, however, including its before-and-after design and the use of steroids in the comparator arm. In addition, little information was available on antibiotics or fluids given at the time of the intervention, according to Dr. Sevransky.

In results of the CITRIS-ALI randomized clinical trial, just published in JAMA, intravenous administration of high-dose vitamin C in patients with sepsis and acute respiratory distress syndrome (ARDS) failed to significantly reduce organ failure scores or biomarkers of inflammation and vascular injury.

In an exploratory analysis of CITRIS-ALI, mortality at day 28 was 29.8% for the treatment group and 46.3% for placebo, with a statistically significant difference between Kaplan-Meier survival curves for the two arms, according to the investigators.

Dr. Sevransky disclosed current grant support from the Biomedical Advanced Research and Development Authority (BARDA) and the Marcus Foundation, as well as a stipend from Critical Care Medicine related to work as an associate editor. He is also a medical adviser to Project Hope and ARDS Foundation and a member of the Surviving Sepsis guideline committees.

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SOURCE: Sevransky J et al. Chest 2019.

ICU automated ventilation outperformed usual care

BY TED BOSWORTH
MDedge News

MADRID – In patients managed on mechanical ventilation in an intensive care unit following cardiac surgery, a fully automated system provides more reliable ventilatory support than highly experienced ICU nurses, suggest results of a randomized trial.

The study's control group received usual care, which means that nurses adjusted mechanical ventilation manually in response to respiratory rate, tidal volume, positive end-respiratory pressure (PEEP), and other factors to maintain ventilation within parameters associated with safe respiration. The experimental group was managed with a fully automated closed-loop system to make these adjustments without any nurse intervention.

Ted Bosworth/MDedge News

Dr. Marcus J. Schultz

For those in the experimental group "the proportion of time in the optimal zone was increased and the proportion of time in the unsafe zone was decreased" relative to those randomized to conventional nursing care, Marcus J. Schultz, MD, reported at the annual congress of the European Respiratory Society.

Conducted at a hospital with an experienced ICU staff, the study had a control arm that was managed by "dedicated nurses who, I can tell you, are very eager to provide the best level of care possible," said Dr. Schultz, professor of experimental intensive care, University of Amsterdam, the Netherlands.

The investigator-initiated POSITiVE trial randomized 220 cardiac surgery patients scheduled to receive postoperative mechanical ventilation in the ICU. Exclusions included those with class III COPD, a requirement for extracorporeal membrane oxygenation (ECMO), or a history of lung surgery.

The primary endpoint was the proportion of time spent in an optimal zone, an acceptable zone, or a dangerous zone of ventilation based on predefined values for tidal volume, maximum airway pressure, end-tidal CO_2, and oxygen saturation (SpO_2).

The greatest between-group difference was seen in the proportion of time spent in the optimal zone. This climbed from approximately 35% in the control arm to slightly more than 70% in the experimental arm, a significant difference. The proportion of time in the dangerous zone was reduced from approximately 6% in the control arm to 3% in the automated arm. On average nurse-managed patients spent nearly 60% of the time in the acceptable zone versus less than 30% for those in the automated experimental arm.

A heat map using green, yellow, and red to represent optimal, acceptable, and dangerous zones, respectively, for individual participants in the trial provided a more stark global impression. For the control group, the heat map was primarily yellow with scattered dashes of green and red. For the experimental group, the map was primarily green with dashes of yellow and a much smaller number of red dashes relative to the control group.

In addition, the time to spontaneous breathing was 38% shorter for those randomized to automated ventilation than to conventional care, a significant difference.

There are now many devices marketed for automated ventilation, according to Dr. Schultz. The device used in this study was the proprietary INTELLiVENT-ASV system, marketed by Hamilton Medical, which was selected based on prior satisfactory experience. Although not unique, this system has sophisticated software to adjust ventilation to reach targets set by the clinician on the basis of information it is receiving from physiologic sensors for such variables as respiratory rate, tidal volume, and inspiratory pressure.

"It is frequently adjusting the PEEP levels to reach the lowest driving pressure," said Dr. Schultz. Among its many other features, it also "gives spontaneous breathing trials automatically."

Uncomplicated patients were selected purposefully to test this system, but Dr. Schultz said that a second trial, called POSITiVE 2, is now being planned that will enroll more complex patients. Keeping complex patients within the optimal zone as defined by tidal volume and other critical variables has the potential to reduce lung damage that is known to occur when these are not optimized.

"Applying safe ventilatory support in clinical practice remains a serious challenge and is extremely time consuming," Dr. Schultz said. He reported that fully automated ventilation appears to be reliable, and "it takes out the human factor" in regard to diligence in monitoring and potential for error.

Overall, these results support the potential for a fully automated system to improve optimal ventilatory support, reduce risk of lung injury, and reduce staffing required for monitoring of mechanical ventilation, according to Dr. Schultz.

Dr. Schultz reports no potential conflicts of interest.

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Lefamulin found noninferior to moxifloxacin for pneumonia

BY HEIDI SPLETE
MDedge News

Oral lefamulin, the first pleuromutilin antibiotic approved for intravenous and oral administration, was noninferior to oral moxifloxacin for inducing an early clinical response in patients with bacterial pneumonia, acording to data from a global multicenter study of 738 individuals.

Persistent high rates of bacterial resistance to current treatments have created the need for more options, especially for the treatment of community-acquired bacterial pneumonia (CABP), which remains a leading cause of hospitalization and death in the United States, wrote Elizabeth Alexander, MD, of Nabriva Therapeutics in King of Prussia, Penn., and colleagues. Lefamulin, "the first pleuromutilin antibiotic approved for intravenous and oral use in humans," has demonstrated activity against many CABP-causing pathogens, including some not susceptible to other classes of antimicrobials, they noted.

Findings of Lefamulin Evaluation Against Pneumonia 2 (LEAP2) were published in JAMA. In this study, the researchers randomized 370 patients to 600 mg of oral lefamulin every 12 hours for 5 days and 368 patients to 400 mg of oral moxifloxacin every 24 hours for 7 days.

Early clinical response rates at 96 hours were 90.8% for both medications (difference of 0.1%). In addition, the rates of clinical response success were similar between the groups in both the modified intent-to-treat population (87.5% with lefamulin and 89.1% with moxifloxacin) and the clinically evaluable population (89.7% with lefamulin and 93.6% with moxifloxacin).

Gastrointestinal issues of diarrhea and nausea were the two most frequently reported treatment-emergent adverse events in both groups. Both conditions occurred more often in the lefamulin group, compared with the moxifloxacin group, but the differences were not significant (12.2% vs. 1.1% and 5.2% vs. 1.9%, respectively).

The study findings were limited by several factors including strict exclusion criteria that may limit the generalizability of the results, as well as a lack of testing for viral copathogens, low recovery of resistant pathogens, and possible misclassification of patient ethnicity, the researchers noted.

However, the results were strengthened by the randomized design, inclusion of patients with more severe CABP, and low rate of discontinuation, they said. The data support previous studies of lefamulin. Its lack of cross-resistance to other drug classes, coverage of typical and atypical CABP pathogens, and options for both oral and intravenous use suggest that it "may provide an alternative approach for the treatment of vulnerable patients," the researchers said.

The study was supported by Nabriva Therapeutics. Dr. Alexander and several coauthors are employees of Nabriva Therapeutics and own stock in the company.

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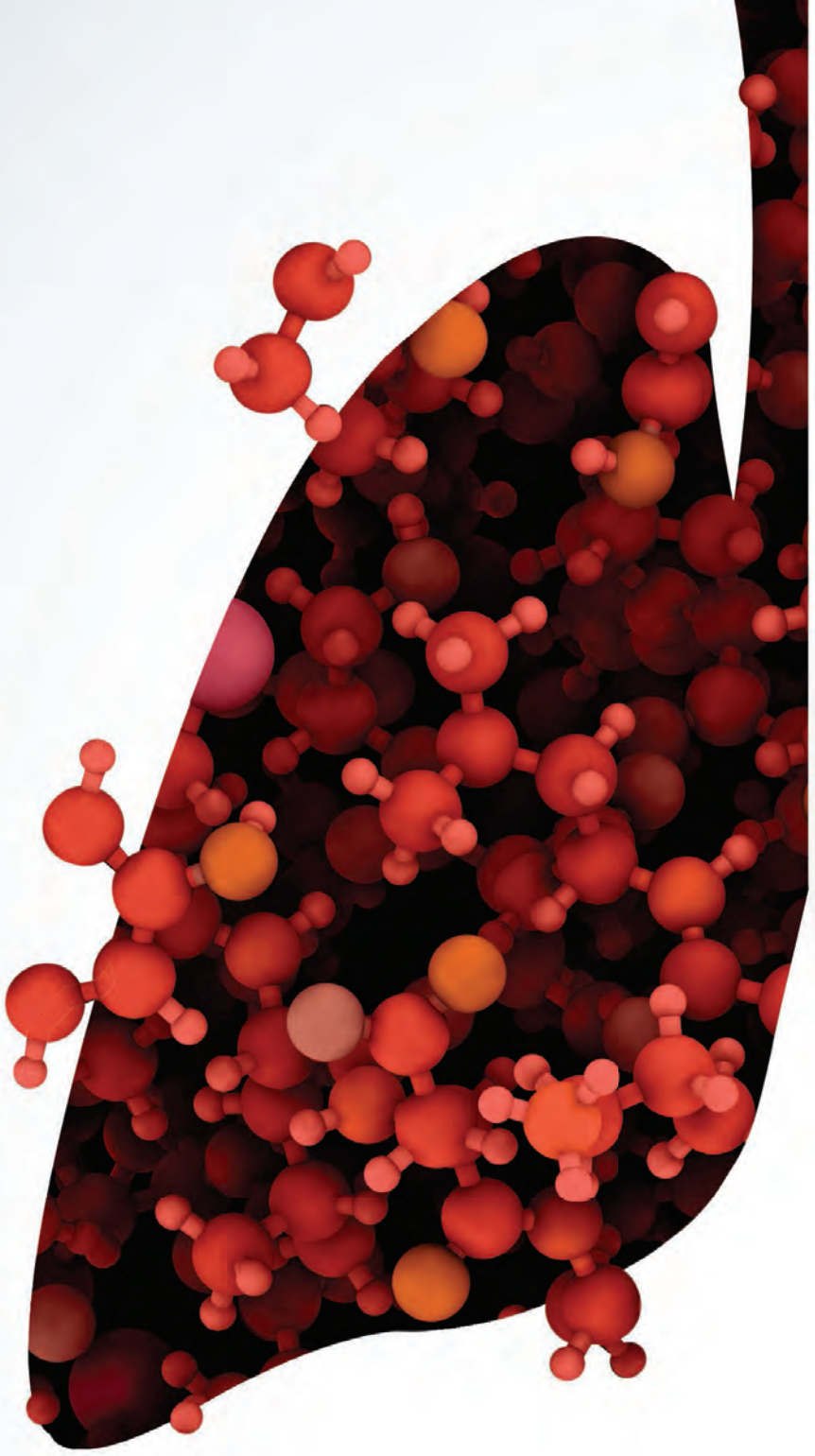
SOURCE: Alexander E et al. JAMA. 2019 Sep 27. doi:10.1001/jama.2019.15468.



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Checklist may improve quality measures in the surgical ICU

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – A standardized checklist may help reduce errors and improve common quality measures in critically ill patients, results of a recent retrospective analysis of 200 consecutive patients suggest.

Use of the checklist was linked to significantly shorter hospital length of stay and ICU length of stay as well as fewer days on a ventilator in the analysis, which was presented at the annual meeting of the American College of Chest Physicians. The 10-item standardized checklist covered a variety topics ranging from comfort, prophylaxis, and sedation to infection control and prevention, nutrition, and medication management review.

Although health economics weren't evaluated in this analysis, changes in those quality measures might also impact the bottom line, according to study coauthor Priscilla Chow, DO, a resident at Suburban Community Hospital in East Norriton, Pa.

"Obviously, if the patient is spending less time in the hospital and fewer days on the ventilator and in the ICU, then we can potentially also be more cost effective in our care," Dr. Chow said in a podium presentation at the meeting.

The use of checklists to standardize processes and reduce errors is a "relatively simple approach" that was adopted from the airline industry and now has been evaluated in a variety of medical care settings, according to Dr. Chow.

Previous studies have demonstrated that checklist-driven care may reduce the incidence of postoperative complications, central line–associated bloodstream infection, ventilator-associated pneumonia, and catheter-associated urinary tract infection.

The present retrospective data analysis by Dr. Chow and colleagues included 200 consecutive patients admitted to the surgical ICU at an urban level 1 trauma center, including 100 patients managed according to the checklist and 100 managed according to standard processes.

Though survival to discharge was comparable between the groups, use of the checklist was associated with a significantly shorter hospital length of stay versus standard care (23.9 vs. 9.5 days). Likewise, the ICU length of stay was shorter in the checklist group (13.0 vs. 6.5 days), and the checklist group had fewer ventilator days (7.7 to 2.8).

Injury Severity Score did not differ between groups; though overall, use of the checklist resulted in more of the underlying topics being addressed in clinical documentation (5.0 vs. 8.7 items).

Dr. Chow and colleagues disclosed that they had no relationships relevant to their study.

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SOURCE: Akella K et al. CHEST 2019. Abstract, doi: 10.1016/j.chest.2019.08.201.

Early palliative care consult decreases in-hospital mortality

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – When initiated early, a palliative care consultation may increase the number of discharges to hospice critical care patients meeting certain end-of-life criteria, results of a recent randomized clinical trial suggest.

The rate of in-hospital mortality was lower for critical care patients receiving an early consultation, compared with those who received palliative care initiated according to usual standards in the randomized, controlled trial, described at the annual meeting of the American College of Chest Physicians.

"There are a lot of things that can get in the way of adequate conversations, and that's when the palliative care team can come in."

More health care surrogates were chosen in the hospital when palliative care medicine was involved earlier, according to investigator Scott Helgeson, MD, fellow in pulmonary critical care at the Mayo Clinic in Jacksonville, Fla.

Taken together, Dr. Helgeson said, those findings suggest the importance of getting palliative care involved "very early, while the patient can still make decisions. ... There are a lot of things that can get in the way of adequate conversations, and that's when the palliative care team can come in," Dr. Helgeson said in an interview.

This study is the first reported to date to look at the impact on patient care outcomes specifically within 24 hours of medical ICU admission, according to Dr. Helgeson and coinvestigators

In their randomized study, patients were eligible if they met at least one of several criteria, including advanced age (80 years or older), late-stage dementia, post–cardiac arrest, metastatic cancer, end-stage organ failure, recurrent ICU admissions, an APACHE II score of 14 or higher, a SOFA score of 9 or higher, preexisting functional dependency, or consideration for a tracheostomy or permanent feeding tube.

Of 29 patients randomized, 14 received early palliative care, and 15 received standard palliative care, which was defined as starting "whenever the treating team deems (it) is appropriate," according to the published abstract.

Hospital mortality occurred in none of the patients in the early palliative care group, versus six in the usual care group ($P = .01$), Dr. Helgeson and colleagues found. Moreover, seven health care surrogates were chosen in hospital in the early palliative care group, versus none in the usual care group (P less than .01).

About one-fifth of deaths in the United States take place in or around ICU admissions, according to the investigators, who noted that those admissions can result in changing goals from cure to comfort – though sometimes too late.

Dr. Helgeson and coauthors disclosed that they had no relationships relevant to this research presentation.

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SOURCE: Helgeson S et al. CHEST 2019 Abstract doi: 10.1016/j.chest.2019.08.803.

FDA approves lefamulin for bacterial CAP in adults

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has announced its approval of lefamulin (Xenleta) for the treatment of community-acquired bacterial pneumonia in adults.

Approval was based on results of two clinical trials assessing a total of 1,289 people with community-acquired bacterial pneumonia. In these trials, lefamulin was compared with moxifloxacin with and without linezolid. Patients who received lefamulin had similar rates of treatment success as those taking moxifloxacin alone or moxifloxacin plus linezolid.

The most common adverse reactions associated with lefamulin include diarrhea, nausea, reactions at the injection site, elevated liver enzymes, and vomiting. Patients with prolonged QT interval, patients with arrhythmias, patients receiving treatment with antiarrhythmic agents, and patients receiving other drugs that prolong the QT interval are contraindicated. In addition, because of evidence of fetal harm in animal studies, pregnant women should be advised of potential risks before receiving lefamulin.

"This new drug provides another option for the treatment of patients with community-acquired bacterial pneumonia, a serious disease. For managing this serious disease, it is important for physicians and patients to have treatment options," Ed Cox, MD, director of the FDA's Office of Antimicrobial Products, said in the press release.

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INDICATIONS AND USAGE
SUNOSI is indicated to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use:
SUNOSI is not indicated to treat the underlying obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI. SUNOSI is not a substitute for these modalities, and the treatment of the underlying airway obstruction should be continued.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS
Blood Pressure and Heart Rate Increases
SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment could be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms
Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders, as SUNOSI has not been evaluated in these patients.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Observe SUNOSI patients for the possible emergence or exacerbation of psychiatric symptoms. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop.

MOST COMMON ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) reported more frequently with the use of SUNOSI than placebo in either narcolepsy or OSA were headache, nausea, decreased appetite, anxiety, and insomnia.

Please see Brief Summary of full Prescribing Information on next page.

Reference: 1. SUNOSI (solriamfetol) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2019.

Jazz Pharmaceuticals

SUNOSI™ (solriamfetol) CIV
75, 150 mg tablets

SUNOSI™ (solriamfetol) tablets, for oral use, CIV
BRIEF SUMMARY OF PRESCRIBING INFORMATION: Consult the Full Prescribing Information for complete product information.
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

SUNOSI is indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use

SUNOSI is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with SUNOSI. SUNOSI is not a substitute for these modalities.

DOSAGE AND ADMINISTRATION

Important Considerations Prior to Initiating Treatment

Prior to initiating treatment with SUNOSI, ensure blood pressure is adequately controlled.

General Administration Instructions

Administer SUNOSI orally upon awakening with or without food. Avoid taking SUNOSI within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.

SUNOSI 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.

CONTRAINDICATIONS

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of monoamine oxidase inhibitor, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS

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SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion.

Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment may be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

SUNOSI has not been evaluated in patients with psychosis or bipolar disorders. Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Patients treated with SUNOSI should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of SUNOSI, consider dose reduction or discontinuation of SUNOSI.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Blood Pressure and Heart Rate Increases
- Psychiatric Symptoms

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SUNOSI has been evaluated in 930 patients (ages 18 to 75 years) with narcolepsy or OSA. Among these patients, 396 were treated with SUNOSI in the 12-week placebo-controlled trials at doses of 37.5 mg (OSA only), 75 mg, and 150 mg once daily. Information provided below is based on the pooled 12-week placebo-controlled studies in patients with narcolepsy or OSA.

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥ 5% and greater than placebo) reported more frequently with the use of SUNOSI than placebo in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, anxiety, and insomnia.

Table 1 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the narcolepsy population.

Table 1: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy (75 mg and 150 mg)

	Narcolepsy	
System Organ Class	**Placebo** N = 108 (%)	**SUNOSI** N = 161 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	9
Psychiatric Disorders		
Insomnia*	4	5
Anxiety*	1	6
Nervous System Disorders		
Headache*	7	16
Cardiac Disorders		
Palpitations	1	2
Gastrointestinal Disorders		
Nausea*	4	7
Dry mouth	2	4
Constipation	1	3

*"Insomnia" includes insomnia, initial insomnia, middle insomnia, and terminal insomnia. "Anxiety" includes anxiety, nervousness, and panic attack. "Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Table 2 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the OSA population.

Table 2: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in OSA (37.5 mg, 75 mg, and 150 mg)

	OSA	
System Organ Class	**Placebo** N = 118 (%)	**SUNOSI** N = 235 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	6
Psychiatric Disorders		
Anxiety*	1	4
Irritability	0	3
Nervous System Disorders		
Dizziness	1	2
Cardiac Disorders		
Palpitations	0	3
Gastrointestinal Disorders		
Nausea*	6	8
Diarrhea	1	4
Abdominal pain*	2	3
Dry mouth	2	3
General Disorders and Administration Site Conditions		
Feeling jittery	0	3
Chest discomfort	0	2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	0	2

*"Anxiety" includes anxiety, nervousness, and panic attack. "Nausea" includes nausea and vomiting. "Abdominal pain" includes abdominal pain, abdominal pain upper, and abdominal discomfort.

Other Adverse Reactions Observed During the Premarketing Evaluation of SUNOSI

Other adverse reactions of < 2% incidence but greater than placebo are shown below. The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have clinically significant implications.

Narcolepsy population:

Psychiatric disorders: agitation, bruxism, irritability

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: hyperhidrosis

General disorders and administration site conditions: feeling jittery, thirst, chest discomfort, chest pain

Investigations: weight decreased

OSA population

Psychiatric disorders: bruxism, restlessness

Nervous system disorders: disturbances in attention, tremor

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Gastrointestinal disorders: constipation, vomiting

Investigations: weight decreased

Dose-Dependent Adverse Reactions

In the 12-week placebo-controlled clinical trials that compared doses of 37.5 mg, 75 mg, and 150 mg daily of SUNOSI to placebo, the following adverse reactions were dose-related: headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth (Table 3).

Table 3: Dose-Dependent Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy and OSA

	Placebo N = 226 (%)	**SUNOSI 37.5 mg** N = 58* (%)	**SUNOSI 75 mg** N = 120 (%)	**SUNOSI 150 mg** N = 218 (%)
Headache**	8	7	9	13
Nausea**	5	7	5	9
Decreased appetite	1	2	7	8
Anxiety	1	2	3	7
Dry mouth	2	2	3	4
Diarrhea	2	2	4	5

*In OSA only.

**"Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Adverse Reactions Resulting in Discontinuation of Treatment

In the 12-week placebo-controlled clinical trials, 11 of the 396 patients (3%) who received SUNOSI discontinued because of an adverse reaction compared to 1 of the 226 patients (< 1%) who received placebo. The adverse reactions resulting in discontinuation that occurred in more than one SUNOSI-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).

Increases in Blood Pressure and Heart Rate

SUNOSI's effects on blood pressure and heart rate are summarized below. Table 4 shows maximum mean changes in blood pressure and heart rate recorded at sessions where the Maintenance of Wakefulness Test (MWT) was administered. Table 5 summarizes 24-hour ambulatory blood pressure monitoring (ABPM) and ambulatory heart rate monitoring performed in the outpatient setting.

Table 4: Maximal Mean Changes in Blood Pressure and Heart Rate Assessed at MWT Sessions from Baseline through Week 12: Mean (95% CI)*

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n	52		51	49	53
	SBP	3.5 (0.7, 6.4)	-	3.1 (0.1, 6.0)	4.9 (1.7, 8.2)	6.8 (3.2, 10.3)
	n	23		47	49	53
	DBP	1.8 (-1.8, 5.5)	-	2.2 (0.2, 4.1)	4.2 (2.0, 6.5)	4.2 (1.5, 6.9)
	n	48		26	49	53
	HR	2.3 (-0.1, 4.7)	-	3.7 (0.4, 6.9)	4.9 (2.3, 7.6)	6.5 (3.9, 9.0)
OSA *STUDY 2*	n	35	17	54	103	35
	SBP	1.7 (-1.4, 4.9)	4.6 (-1.1, 10.2)	3.8 (1.2, 6.4)	2.4 (0.4, 4.4)	4.5 (1.1, 7.9)
	n	99	17	17	107	91
	DBP	1.4 (-0.1, 2.9)	1.9 (-2.3, 6.0)	3.2 (-0.9, 7.3)	1.8 (0.4, 3.2)	3.3 (1.8, 4.8)
	n	106	17	51	102	91
	HR	1.7 (0.1, 3.3)	1.9 (-1.9, 5.7)	3.3 (0.6, 6.0)	2.9 (1.4, 4.4)	4.5 (3.0, 6.0)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*For study weeks 1, 4, and 12, SBP, DBP, and HR were assessed pre-dose and every 1-2 hours for 10 hours after test drug administration. For all time points at all visits, the mean change from baseline was calculated, by indication and dose, for all patients with a valid assessment. The table shows, by indication and dose, the mean changes from baseline for the week and time point with the maximal change in SBP, DBP, and HR.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Table 5: Blood Pressure and Heart Rate by 24-hour Ambulatory Monitoring: Mean Change (95% CI) from Baseline at Week 8

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n*	46		44	44	40
	SBP	-0.4 (-3.1, 2.4)	-	1.6 (-0.4, 3.5)	-0.5 (-2.1, 1.1)	2.4 (0.5, 4.3)
	DBP	-0.2 (-1.9, 1.6)	-	1.0 (-0.4, 2.5)	0.8 (-0.4, 2.0)	3.0 (1.4, 4.5)
	HR	0.0 (-1.9, 2.0)	-	0.2 (-2.1, 2.4)	1.0 (-1.2, 3.2)	4.8 (2.3, 7.2)
OSA *STUDY 2*	n*	92	43	49	96	84
	SBP	-0.2 (-1.8, 1.4)	1.8 (-1.1, 4.6)	2.6 (0.02, 5.3)	-0.2 (-2.0, 1.6)	2.8 (-0.1, 5.8)
	DBP	0.2 (-0.9, 1.3)	1.4 (-0.4, 3.2)	1.5 (-0.04, 3.1)	-0.1 (-1.1, 1.0)	2.4 (0.5, 4.4)
	HR	-0.4 (-1.7, 0.9)	0.4 (-1.4, 2.2)	1.0 (-0.9, 2.81)	1.7 (0.5, 2.9)	1.6 (0.3, 2.9)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*Number of patients who had at least 50% valid ABPM readings.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors

Do not administer SUNOSI concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

Drugs that Increase Blood Pressure and/or Heart Rate

Concomitant use of SUNOSI with other drugs that increase blood pressure and/or heart rate has not been evaluated, and such combinations should be used with caution.

Dopaminergic Drugs

Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with SUNOSI. Interactions with dopaminergic drugs have not been evaluated with SUNOSI. Use caution when concomitantly administering dopaminergic drugs with SUNOSI.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SUNOSI during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at *www.SunosiPregnancyRegistry.com*.

Risk Summary

Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ 4 and 5 times and was teratogenic at doses 19 and ≥ 5 times, respectively, the maximum recommended human dose (MRHD) of 150 mg based on mg/m^2 body surface area. Oral administration of solriamfetol to pregnant rats during pregnancy and lactation at doses ≥ 7 times the MRHD based on mg/m^2 body surface area resulted in maternal toxicity and adverse effects on fertility, growth, and development in offspring *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Solriamfetol was administered orally to pregnant rats during the period of organogenesis at 15, 67, and 295 mg/kg/day, which are approximately 1, 4, and 19 times the MRHD based on mg/m^2 body surface area. Solriamfetol at ≥ 4 times the MRHD caused maternal toxicity that included hyperactivity, significant decreases in body weight, weight gain, and food consumption. Fetal toxicity at these maternally toxic doses included increased incidence of early resorption and post-implantation loss, and decreased fetal weight.

Solriamfetol was teratogenic at 19 times the MRHD; it increased the incidence of fetal malformations that included severe sternebrae mal-alignment, hindlimb rotation, bent limb bones, and situs inversus. This dose was also maternally toxic. The no-adverse-effect level for malformation is 4 times and for maternal and embryofetal toxicity is approximately 1 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rabbits during the period of organogenesis at 17, 38, and 76 mg/kg/day, which are approximately 2, 5, and 10 times the MRHD based on mg/m^2 body surface area. Solriamfetol at 10 times the MRHD caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥ 5 times the MRHD, it caused fetal skeletal malformation (slight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for malformation and fetal toxicity is approximately 2 times and for maternal toxicity is approximately 5 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 post-partum, at 35, 110, and 350 mg/kg/day, which are approximately 2, 7, and 22 times the MRHD based on mg/m^2 body surface area. At ≥ 7 times the MRHD, solriamfetol caused maternal toxicity that included decreased body weight gain, decreased food consumption, and hyperpnea. At these maternally toxic doses, fetal toxicity included increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. Developmental toxicity in offspring after lactation day 20 included decreased body weight, decreased weight gain, and delayed sexual maturation. Mating and fertility of offspring were decreased at maternal doses 22 times the MRHD without affecting learning and memory. The no-adverse-effect level for maternal and developmental toxicity is approximately 2 times the MRHD based on mg/m^2 body surface area.

LACTATION

Risk Summary

There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.

Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition.

Clinical Considerations

Monitor breastfed infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of SUNOSI in pediatric patients have not been conducted.

Geriatric Use

Of the total number of patients in the narcolepsy and OSA clinical studies treated with SUNOSI, 13% (123/930) were 65 years of age or over.

No clinically meaningful differences in safety or effectiveness were observed between elderly and younger patients.

Solriamfetol is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

Renal Impairment

Dosage adjustment is not required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2). Dosage adjustment is recommended for patients with moderate to severe renal impairment (eGFR 15-59 mL/min/1.73 m^2). SUNOSI is not recommended for patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SUNOSI contains solriamfetol, a Schedule IV controlled substance.

Abuse

SUNOSI has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of SUNOSI 300 mg, 600 mg, and 1200 mg (two, four, and eight times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg and 90 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals experienced with the recreational use of stimulants. Results from this clinical study demonstrated that SUNOSI produced Drug Liking scores similar to or lower than phentermine. In this crossover study, elevated mood was reported by 2.4% of placebo-treated subjects, 8 to 24% of SUNOSI-treated subjects, and 10 to 18% of phentermine-treated subjects. A 'feeling of relaxation' was reported in 5% of placebo-treated subjects, 5 to 19% of SUNOSI-treated subjects and 15 to 20% of phentermine-treated subjects.

Physicians should carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant (e.g., methylphenidate, amphetamine, or cocaine) or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of SUNOSI (e.g., incrementation of doses, drug-seeking behavior).

Dependence

In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of SUNOSI were evaluated following at least 6 months of SUNOSI use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of SUNOSI were also evaluated during the two-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of SUNOSI resulted in a consistent pattern of adverse events in individual subjects that was suggestive of physical dependence or withdrawal.

OVERDOSAGE

A specific reversal agent for SUNOSI is not available. Hemodialysis removed approximately 21% of a 75 mg dose in end stage renal disease patients. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring.

Consult with a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Potential for Abuse and Dependence

Advise patients that SUNOSI is a federally controlled substance because it has the potential to be abused. Advise patients to keep their medication in a secure place and to dispose of unused SUNOSI as recommended in the Medication Guide.

Primary OSA Therapy Use

Inform patients that SUNOSI is not indicated to treat the airway obstruction in OSA and they should use a primary OSA therapy, such as CPAP, as prescribed to treat the underlying obstruction. SUNOSI is not a substitute for primary OSA therapy.

Blood Pressure and Heart Rate Increases

Instruct patients that SUNOSI can cause elevations of their blood pressure and pulse rate and that they should be monitored for such effects.

Psychiatric Symptoms

Instruct patients to contact their healthcare provider if they experience, anxiety, insomnia, irritability, agitation, or signs of psychosis or bipolar disorders.

Lactation

Monitor breastfed infants for adverse reactions such as agitation, insomnia, anorexia, and reduced weight gain.

For more information, visit www.SUNOSI.com

Distributed by:
Jazz Pharmaceuticals, Inc. Palo Alto, CA 94304
Protected by U.S. patent numbers: 8440715, 8877806, and 9604917
Revised: 06/2019

Newly described lung disorder strikes children with systemic juvenile idiopathic arthritis

BY MICHELE G. SULLIVAN
MDedge News

An uncommon but potentially deadly inflammatory lung disease is emerging among children with systemic juvenile idiopathic arthritis, and its history appears to coincide with the rise of powerful biologics as first-line therapy for children with the disease.

Most confirmed cases of systemic juvenile idiopathic arthritis with lung disease (sJIA-LD) are in the United States. But it's popping up in other places that have adopted early biologic treatment for sJIA – including Canada, South America, Europe, and the Middle East.

The respiratory symptoms are relatively subtle, so by the time of lung disease detection, the amount of affected lung can be extensive, said Elizabeth Mellins, MD, a Stanford (Calif.) University researcher who, along with first author Vivian Saper, MD, recently published the largest case series comprising reports from 37 institutions (Ann Rheum Dis. 2019 Sep 27. doi: 10.1136/annrheumdis-2019-216040). By the end of follow-up, 22 of the 61 children in her cohort had died, including all 12 patients who demonstrated excessively high neutrophil levels in bronchoalveolar lavage samples.

Another recent report, authored by Grant Schulert, MD, PhD, and colleagues of the Cincinnati Children's Hospital Medical Center, described 18 patients, 9 of whom were also included in the Stanford cohort (Arthritis Rheumatol. 2019 Aug 5. doi: 10.1002/art.41073).

Both investigators have now identified new patients.

"We are aware of 60 additional cases beyond what were included in our series," Dr. Mellins said in an interview, bringing her entire cohort to 121. Dr. Schulert also continues to expand his group, detailing nine new cases at a recent private meeting.

"We are up to 27 now," he said. "The features of these new patients are all very similar: The children are very young, all have had macrophage activation syndrome in the past and very-difficult-to-control JIA. Reactions to tocilizumab [Actemra] were also not uncommon in this group."

Dr. Mellins also saw this association with allergic-type tocilizumab reactions, severe delayed hypersensitivity reactions to anakinra (Kineret) or canakinumab (Ilaris). Although serious lung disease in sJIA patients is not unheard of, this phenotype was virtually unknown until about a decade ago. Both investigators said that it's been rising steadily since 2010 – just about the time that powerful cytokine-inhibiting biologics were changing these patients' world for the better. After decades of relying almost solely on steroids and methotrexate, with rather poor results and significant long-term side effects, children were not only improving, but thriving. Gone was the life-changing glucocorticoid-related growth inhibition. Biologics could halt fevers, rash, and joint destruction in their tracks.

Courtesy Dr. Elizabeth Mellins

Dr. Vivian Saper (left) and Dr. Elizabeth Mellins

But the emergence of this particular type of lung disease could throw a pall over that success story, he said. If sJIA-LD is temporally associated with increasing reliance on long-term interleukin-1/IL-6 inhibition in children with early-onset disease, could these drugs actually be the causative agent?

Some of the 18 in his initial series have improved, while 36% of those in the Stanford series died. Most who do recover stay on their IL-1 or IL-6–blocking therapy with good disease control without further lung problems. Both investigators found compelling genetic hints, but nothing conclusive. Children with trisomy 21 appear especially vulnerable. Most patients are very young – around 2 years old – but others are school aged. Some had a history of macrophage activation syndrome. Some had hard-to-control disease and some were clinically well controlled when the lung disease presented.

With so many potential links, all unproven, clinicians may question the wisdom of embarking on long-term biologic therapy for their children with sJIA. Peter Nigrovic, MD, of Boston Children's Hospital, addressed this in an accompanying editorial (Arthritis Rheumatol. 2019 Aug 7. doi: 10.1002/art.41071).

"My take on this is that it's a very worrisome trend," he said in an interview. "We've been going full bore toward early biologic therapy in sJIA and at the same time we are seeing more of this lung disease. Is it guilt by association? Or is there something more? The challenge for us is not to jump too soon to that conclusion."

Although the association is there, he said, association does not equal causation. And there's no doubt that biologics have vastly improved the lives of sJIA patients. "The drugs might be causal, and I worry about that and think we need to study it. But we absolutely need stronger evidence before we change practice."

"This is a new manifestation of the disease, and it's coming at the same time we are changing the treatment paradigm," Dr. Nigrovic continued. "It could be because of interleukin-1 or interleukin-6 blockade. There is biological plausibility for such a link. It could also be related to the fact that we are using less steroids and methotrexate, which might have been preventing this. The appearance of sJIA lung disease could also be that a distinct secular trend unrelated to treatment, just as we saw amyloid come and go in this population in Europe. These other therapies were actually preventing this. We just don't know."

Clinical characteristics

Children presented with similar symptoms. Respiratory symptoms are usually subtle and mild. These can include tachypnea, hypoxia (43% in the Stanford series), and pulmonary hypertension (30% in the Stanford series).

Digital clubbing, often with erythema, was a common finding. Some children showed pruritic, nonevanescent rashes. Eosinophilia occurred in 37% of the Stanford series and severe abdominal pain in 16%, although Dr. Mellins noted that belly pain may be underestimated, as it was only volunteered, not queried, information.

"There are some red flags that should raise suspicion even without obvious respiratory symptoms," Dr. Mellins said. These include lymphopenia, unexplained abdominal pain, eosinophilia, an unusual rash, and finger clubbing with or without erythema.

Findings on imaging were consistent in both series. Several key clinic features emerged: pleural thickening, septal thickening, bronchial wall or peribronchovascular thickening, "tree-in-bud" opacities, "ground-glass" opacities, peripheral consolidation, and lymphadenopathy.

The research groups were supported by grants from the sJIA Foundation, the Lucile Packard Foundation for Children's Health, Stanford graduate fellowships, the Life Sciences Research Foundation, the Bill & Melinda Gates Foundation, Cincinnati Children's Research Foundation, the Childhood Arthritis and Rheumatology Research Alliance, the Arthritis Foundation, and the National Institutes of Health. Many authors on both papers reported financial ties to Genentech, which markets tocilizumab, and other pharmaceutical companies. Dr. Nigrovic reported receiving consulting fees and research support from Novartis and other companies.

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SOURCES: Saper V et al. Ann Rheum Dis. 2019 Sep 27. doi: 10.1136/annrheumdis-2019-216040; Schulert G et al. Arthritis Rheumatol. 2019 Aug 5. doi: 10.1002/art.41073; Nigrovic P Arthritis Rheumatol. 2019 Aug 7. doi: 10.1002/art.41071.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: More information is needed for this new and rare but important interstitial lung disease. The Children's Interstitial and Diffuse Lung Disease Research Network and the chILD Foundation are important groups that help support pediatric interstitial lung disease research and patients. Pulmonary alveolar proteinosis (PAP), specifically, is an interstitial lung disease that can occur in children and adults. Acquired PAP can occur, for example, in firefighters, amyloidosis. This research points to a new cause of lung disease that appears to be very similar to PAP.

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NAM offers recommendations to fight clinician burnout

BY KERRY DOOLEY YOUNG
MDedge News

WASHINGTON – The practice of medicine needs a major reset to address the stresses that lead to clinician burnout, a condition now estimated to affect one-third to one-half of clinicians in the United States, according to a report from an influential federal panel.

On Oct. 23, the National Academy of Medicine (NAM) released a report, "Taking Action Against Clinician Burnout: A Systems Approach to Professional Well-Being." The report calls for a broad and unified approach to tackling the root causes of burnout.

There must be a concerted effort by leaders of many fields of health care to create less stressful workplaces for clinicians, Pascale Carayon, PhD, cochair of the NAM committee that produced the report, said during the NAM press event.

"This is not an easy process," said Dr. Carayon, a researcher into patient safety issues at the University of Wisconsin–Madison. "There is no single solution."

The NAM report assigns specific tasks to many different participants in health care through a six-goal approach, as described below.

• Create positive workplaces. Leaders of health care systems should consider how their business and management decisions will affect clinicians' jobs, taking into account the potential to add to their levels of burnout. Executives need to continuously monitor and evaluate the extent of burnout in their organizations, and report on this at least annually.

• Address burnout in training and in clinicians' early years. Medical, nursing, and pharmacy schools should consider steps such as monitoring workload, implementing pass-fail grading, improving access to scholarships and affordable loans, and creating new loan repayment systems.

• Reduce administrative burden. Federal and state bodies and organizations such as the National Quality Forum should reconsider how their regulations and recommendations contribute to burnout. Organizations should seek to eliminate tasks that do not improve the care of patients.

• Improve usability and relevance of health information technology (IT). Medical organizations should develop and buy systems that are as user-friendly and easy to operate as possible. They also should look to use IT to reduce documentation demands and automate nonessential tasks.

Dr. Vindell Washington

• Reduce stigma and improve burnout recovery services. State officials and legislative bodies should make it easier for clinicians to use employee assistance programs, peer support programs, and mental health providers without the information being admissible in malpractice litigation. The report notes the recommendations from the Federation of State Medical Boards, American Medical Association, and the American Psychiatric Association on limiting inquiries in licensing applications about a clinician's mental health. Questions should focus on current impairment rather than reach well into a clinician's past.

• Create a national research agenda on clinician well-being. By the end of 2020, federal agencies – including the Agency for Healthcare Research and Quality, the National Institute for Occupational Safety and Health, the Health Resources and Services Administration, and the U.S. Department of Veterans Affairs – should develop a coordinated research agenda on clinician burnout, the report said.

In casting a wide net and assigning specific tasks, the NAM report seeks to establish efforts to address clinician burnout as a broad and shared responsibility. It would be too easy for different medical organizations to depict addressing burnout as being outside of their responsibilities, Christine K. Cassel, MD, the cochair of the NAM committee that produced the report, said during the press event.

"Nothing could be farther from the truth. Everyone is necessary to solve this problem," said Dr. Cassel, who is a former chief executive officer of the National Quality Forum.

Darrell G. Kirch, MD, chief executive of the Association of American Medical Colleges, described the report as a "call to action" at the press event.

Previously published research has found between 35% and 54% of nurses and physicians in the United States have substantial symptoms of burnout, with the prevalence of burnout ranging between 45% and 60% for medical students and residents, the NAM report said.

Leaders of health organizations must consider how the policies they set will add stress for clinicians and make them less effective in caring for patients, said Vindell Washington, MD, chief medical officer of Blue Cross Blue Shield of Louisiana and a member of the NAM committee that wrote the report.

"Those linkages should be incentives and motivations for boards and leaders more broadly to act on the problem," Dr. Washington said at the NAM event.

Dr. Kirch said he experienced burnout as a first-year medical student. He said a "brilliant aspect" of the NAM report is its emphasis on burnout as a response to the conditions under which medicine is practiced. In the past, burnout has been viewed as being the fault of the physician or nurse experiencing it, with the response then being to try to "fix" this individual, Dr. Kirch said at the event.

The NAM report instead defines burnout as a "work-related phenomenon studied since at least the 1970s," in which an individual may experience exhaustion and detachment. Depression and other mental health issues such as anxiety disorders and addiction can follow burnout, he said. "That involves a real human toll."

Joe Rotella, MD, MBA, chief medical officer at American Academy of Hospice and Palliative Medicine, said in an interview that this NAM paper has the potential to spark the kind of transformation that its earlier research did for the quality of care. Then called the Institute of Medicine, NAM in 1999 issued a report, "To Err Is Human," which is broadly seen as a key catalyst in efforts in the ensuing decades to improve the quality of care. IOM then followed up with a 2001 report, "Crossing the Quality Chasm."

"Those papers over a period of time really did change the way we do health care," said Dr. Rotella, who was not involved with the NAM report.

In Dr. Rotella's view, the NAM report provides a solid framework for what remains a daunting task, addressing the many factors involved in burnout.

"The most exciting thing about this is that they don't have 500 recommendations. They had six and that's something people can organize around," he said. "They are not small goals. I'm not saying they are simple."

The NAM report delves into the factors that contribute to burnout. These include a maze of government and commercial insurance plans that create "a confusing and onerous environment for clinicians," with many of them juggling "multiple payment systems with complex rules, processes, metrics, and incentives that may frequently change."

Clinicians face a growing field of measurements intended to judge the quality of their performance. While some of these are useful, others are duplicative and some are not relevant to patient care, the NAM report said.

The report also noted that many clinicians describe electronic health records as taking a toll on their work and private lives. Previously published research has found that, for every hour spent with a patient, physicians spend an additional 1-2 hours on the EHR at work, with additional time needed to complete this data entry at home after work hours, the report said.

In an interview, Cynda Rushton, RN, PhD, a Johns Hopkins University researcher and a member of the NAM committee that produced the report, said this new publication will support efforts to overhaul many aspects of current medical practice. She said she hopes it will be a "catalyst for bold and fundamental reform.

"It's taking a deep dive into the evidence to see how we can begin to dismantle the system's contributions to burnout," she said. "No longer can we put Band-Aids on a gaping wound."

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Judge rules for insurer in doctor's allocation lawsuit

BY ALICIA GALLEGOS
MDedge News

A judge has sided with a medical malpractice insurer in a legal challenge that accused the company of misallocating blame among physicians after a liability settlement.

In a Sept. 27 decision, Judge Debra Squires-Lee of the Commonwealth of Massachusetts Superior Court ruled that Medical Professional Mutual Insurance Company (ProMutual) acted reasonably when it settled a medical liability claim for $500,000 against several health providers and allocated responsibility for 30% of the settlement ($150,000) to internist Nataly Minkina, MD. ProMutual was well within its rights and obligations when it settled the underlying claim and did not act in bad faith when assigning responsibility in the case, Judge Squires-Lee wrote in her 49-page ruling.

"At its heart, this case is about a multiple defendant malpractice lawsuit with finger pointing by Dr. Minkina against her codefendants and others, and a disagreement about ProMutual's ultimate determination about how to allocate a global settlement with the plaintiffs amongst ProMutual's insureds," Judge Squires-Lee wrote in the decision. "Dr. Minkina strongly believes that she did not fail [the patient], that she acted reasonably, and that her treatment of [the patient] satisfied the standard of care. She also questions why ProMutual failed to allocate liability in the [patient's] suit to other physicians. However ... the question for this court is whether ProMutual committed unfair or deceptive acts or practices in its settlement and allocation of its settlement. I conclude that ProMutual did not."

The case stems from a patient's lawsuit against Dr. Minkina and several others at Blue Hills Medical Associates in Braintree, Mass.

The patient alleged that the health care professionals were responsible for a missed breast cancer diagnosis. Dr. Minkina saw the patient just once in 2002 while covering for another doctor. During the visit, she confirmed some nodularity in the 55-year-old women's breast and referred her for a mammogram and an ultrasound. A radiologist twice reported no abnormalities, which Dr. Minkina said she relayed to the patient. Dr. Minkina left the practice shortly after.

The patient visited the practice several more times and was referred for another mammogram in 2006, the results of which revealed some signs of malignancy, according to court documents. However, a nurse at the practice misread, misunderstood, or overlooked the signs and recorded that "the benign breast condition had no changes," according to court transcripts. Later that year, the patient visited the practice complaining of headaches and a droopy eye at which time her primary care physician diagnosed sinusitis and prescribed antibiotics. In 2007, the patient underwent MRIs of the brain and the breast, which revealed widespread metastatic carcinoma. She and her family sued Dr. Minkina and several others in June 2007. The patient died in 2008.

ProMutual settled the case against the defendants for $500,000 in 2008, allocating 30% of the liability to Dr. Minkina, 10% of the nurse practitioner, 60% to the medical practice, and no liability to the other doctors named. ProMutual contended Dr. Minkina bore more responsibility than the other health care professionals named for the delayed diagnosis because of causation factors and standard of care violations, namely that Dr. Minkina should have pursued a biopsy for the patient.

Dr. Minkina sued the insurer in 2012, claiming chiefly that the insurer allocated an unjustifiably high percentage of liability to her because she was no longer insured and because the company had an economic incentive to allocate a disproportionate percentage of responsibility and damages.

A lower court initially dismissed Dr. Minkina's suit, but the Commonwealth of Massachusetts Appeals Court in 2015 overturned that decision, ruling the case could move forward. In 2018, the superior court agreed Dr. Minkina had a valid bad faith claim, stating that she had provided information about ProMutual's conduct from which "a reasonable juror could infer the defendant's bad faith in connection with its settling the underlying malpractice suit, including the allocation of liability.

But Judge Squires-Lee ruled that trial evidence showed that ProMutual did not act for its own benefit or favor other insureds over Dr. Minkina. The judge wrote that the insurer satisfied its contractual and legal obligations when defending the underlying legal claim.

Dr. Minkina said she was disappointed with the ruling, but that she is considering her legal avenues.

ProMutual declined to comment about the decision.

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President to nominate oncologist to lead FDA

BY ALICIA GALLEGOS
MDedge News

Stephen M. Hahn, MD, a radiation oncologist and researcher, may soon take the reins of the Food and Drug Administration.

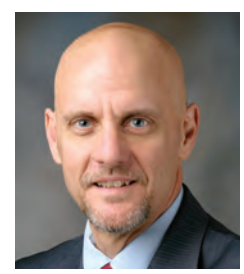
President Trump indicated his intent to nominate Dr. Hahn as FDA Commissioner in a brief Nov.1 statement that outlined Dr. Hahn's background. Dr. Hahn currently serves as chief medical executive at MD Anderson Cancer Center, Houston, where he heads the radiology oncology division.

Dr. Hahn specializes in treating lung cancer and sarcoma and has authored 220 peer-reviewed original research articles. He was previously chair of the department of radiology oncology at the University of Pennsylvania, Philadelphia, and also served as a senior investigator at the National Cancer Institute.

Dr. Hahn completed his residency in radiation oncology at NCI and his residency in internal medicine at the University of California, San Francisco.

Margaret Foti, PhD, chief executive officer for the American Association for Cancer Research called Dr. Hahn a renowned expert in radiation oncology and research, an experienced and highly effective administrator, and an innovative leader.

"I have seen firsthand Dr. Hahn's extraordinary dedication and commitment to cancer patients, and the AACR is extremely confident that he will be an outstanding leader for the FDA," Dr. Foti said in a statement. "Dr. Hahn, who is board certified in both radiation and medical oncology, is esteemed for the breadth and depth of his scientific knowledge and expertise, and he has consistently advocated for a drug review process at the FDA that is both science directed and patient focused."



Dr. Hahn

The American Society of Clinical Oncology also congratulated Dr. Hahn on the upcoming nomination, noting that he has a strong grasp of the drug development process and understands the realities of working in a complex clinical care environment.

"The role of FDA commissioner requires a strong commitment to advancing the agency's mission to protect public health across the United States, and an understanding of how to help speed innovations to get new treatments to patients, while also ensuring the safety and efficacy of the medical products that millions of Americans rely on to manage, treat, and cure their cancer," the society stated. "ASCO has a long and productive history of collaborating with FDA, including with current Acting Commissioner, Ned Sharpless, MD, in support of the agency's important role in reducing cancer incidence, advancing treatment options, and improving the lives of individuals with cancer. We look forward to continuing our close collaboration to make it possible for every American with cancer to have access to medical products that are safe and effective."

Dr. Sharpless will return to his position as NCI director; he served as interim FDA commissioner from the April departure of then-FDA commissioner, Scott Gottlieb, MD.

"As one of the nation's leading oncologists who has devoted his entire professional career to helping patients in the fight against cancer, Ned is returning home to NCI to continue this work and we look forward to working closely with him once again," Francis S. Collins, MD, director of the National Institutes of Health, said in a statement. "

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Demeaning patient behavior takes emotional toll on physicians

BY STEVE CIMINO
MDedge News

Despite an increasingly diverse workforce, a new study has found that many patients remain biased toward certain physicians, which can produce substantial negative – and occasionally positive – effects.

"Addressing demeaning behavior from patients will require a concerted effort from medical schools and hospital leadership to create an environment that respects the diversity of patients and physicians alike," wrote Margaret Wheeler, MD, of the University of California, San Francisco and her coauthors. The study was published in JAMA Internal Medicine.

To determine the perspectives of physicians and trainees in regard to patient bias, along with potential barriers to responding effectively, the researchers led 13 focus groups attended by 11 internal medicine hospitalist physicians, 26 internal medicine residents, and 13 medical students affiliated with the UCSF School of Medicine.

In describing biased and demeaning patient behavior, the participants recalled remarks that ranged from refusal of care and questioning the clinician's role to ethnic jokes, questions as to their ethnic backgrounds, and inappropriate flirtations or compliments. The effects of these behaviors on the participants included negative responses like carrying an emotional burden and withdrawing from work, along with positive responses like an increased desire for self-growth and to pursue leadership opportunities.

Barriers to addressing these behaviors included a lack of support, uncertainty as to the appropriate response, and a fear of being perceived as unprofessional. Deciding how to respond – or to respond at all – was often dictated by the level of support from colleagues, a professional responsibility to peers, and the presence of a positive role model who would've done the same.

The study was supported by the Greenwall Foundation. The authors reported no conflicts of interest.

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SOURCE: Wheeler M et al. JAMA Intern Med. 2019 Oct 28. doi: 10.1001/jamainternmed.2019.4122.

VIEW ON THE NEWS

The results of the patient bias study from Wheeler et al. are troubling, but not surprising. As the physician workforce becomes more diverse in regard to race, ethnicity, sex, gender identity, and sexual orientation, considering and addressing the negative impacts of demeaning patient interactions becomes increasingly important. And though a recent analysis stated a decline in biases between 2007 and 2016, discriminatory and disrespectful treatment remains the norm for members of many minority groups.

Strategies to address these behaviors include codes of professional ethics offering guidance on responding to disrespectful behavior, antidiscrimination training for all health professionals, and health care leaders themselves practicing and preaching respectfulness and civility within their institutions. Patients can be expected to behave respectfully towards physicians only if the culture of health care is also respectful. When anyone, including a patient, exhibits biased and disrespectful behavior, silence is not golden. It is tacit approval. We all have the responsibility to speak and act.

Lisa A. Cooper, MD, and Mary Catherine Beach, MD, of Johns Hopkins University in Baltimore; and David R. Williams, PhD, of Harvard University, Boston, made these comments in an accompanying editorial (JAMA Intern Med. 2019 Oct 28. doi: 10.1001/jamainternmed.2019.4100). They reported no conflicts of interest.

Judge dismisses doctors' lawsuit against ABIM

BY ALICIA GALLEGOS
MDedge News

A district court has dismissed a lawsuit levied by a group of physicians against the American Board of Internal Medicine (ABIM) over its maintenance of certification (MOC) program, calling the legal challenge "flawed."

In a Sept. 26 decision, U.S. District Court Judge for the Eastern District of Pennsylvania Robert F. Kelly Sr. said the plaintiffs failed to demonstrate sufficient evidence for their antitrust and unjust enrichment claims against ABIM. The doctors also did not establish any showing of anticompetitive conduct by ABIM to support a monopolization claim, the judge ruled.

"We disagree with plaintiffs and find that ABIM's initial certification and MOC products are part of a single product and do not occupy distinct markets," Judge Kelly wrote in his decision. "Not only are we unconvinced by plaintiffs' arguments, we find that plaintiffs' entire framing of the ABIM certification to be flawed. In essence, plaintiffs are arguing that, in order to purchase ABIM's initial certification, internists are forced to purchase MOC products as well. However, this is not the case. ... Nowhere in the amended complaint do plaintiffs allege that they were forced to buy MOC products in order to purchase the initial certification."

The judge dismissed the suit, but allowed the plaintiffs 14 days to submit an amended complaint reoutlining their claims of illegal monopolization and racketeering against the board. If the amended complaint passes legal muster, the judge could revive those claims.

ABIM President Richard J. Baron, MD, expressed satisfaction that the court granted the board's motion to dismiss the case for failure to state a valid claim.

"ABIM is pleased that the United States District Court for the Eastern District of Pennsylvania dismissed in its entirety a lawsuit that alleged physicians were harmed by the requirements for maintaining ABIM board certification," Dr. Baron said in a statement.

C. Philip Curley, a Chicago-based attorney for the physician plaintiffs, said the case is far from over.

"The four internists who brought the lawsuit were invited to file amended claims, which is certainly being considered," Mr. Curley said in an interview.

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NEWS FROM CHEST

This month in the journal *CHEST*®

Editor's Picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Editorials

Preventing Patient and Physician Harm.
By Dr. J. D.Zibrak

Intensivist Burnout: Running on Empty?
By Dr. Curtis N. Sessler

Original Research

Medical Malpractice Involving Pulmonary/Critical Care Physicians.
By Dr. L. C. Myers, et al.

Impaired Sleep Quality in COPD Is Associated With Exacerbations: The CanCOLD Cohort Study.
By Dr. M. Shorofsky et al.

INDICATION

TRELEGY is for maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

TRELEGY is NOT indicated for relief of acute bronchospasm or asthma.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- TRELEGY is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate (FF), umeclidinium (UMEC), vilanterol (VI), or any of the excipients.

WARNINGS AND PRECAUTIONS

- TRELEGY is not for the treatment of asthma. Long-acting beta$_2$-adrenergic agonist (LABA) monotherapy for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with inhaled corticosteroids (ICS), data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- TRELEGY is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- TRELEGY should not be used more often or at higher doses than recommended or with another LABA for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.

Please see additional Important Safety Information for TRELEGY throughout.

Please see Brief Summary of Prescribing Information for TRELEGY following this ad.

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TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

TODAY. TOMORROW. TRELEGY.

TRELEGY: Rapid and lasting improvements in lung function

As early as 15 MINUTES...

Maintained for 24 HOURS

- TRELEGY provided improvement in FEV_1 vs BREO, as measured by LS mean change from baseline in FEV_1 beginning at 15 minutes on Day 1[1]
- Improvement persisted for 24 hours on Day 1 and Day 84[1]

In 2 replicate studies, the primary efficacy endpoint was trough FEV_1 at Day 85. The LS mean change from baseline in trough FEV_1 at Day 85 for TRELEGY (n=206 in each trial) vs placebo + BREO (n=206 in each trial) was 124 mL for Trial 1 and 122 mL for Trial 2.[1]

TRELEGY is not a rescue inhaler and should not be used for the relief of acute symptoms.

TRIALS 1 AND 2 STUDY DESCRIPTION[1,2]

Design: Two 12-week, randomized, double-blind, parallel-group multicenter studies were conducted to evaluate the efficacy and safety of INCRUSE or placebo added to BREO 100/25. Treatment with TRELEGY refers to patients who received INCRUSE added to BREO 100/25. Eligible patients entered a 4-week open-label run-in period following screening where they received BREO 100/25. Patients were then randomized to receive INCRUSE (n=206 in each trial) or placebo (n=206 in each trial) added to open-label BREO 100/25.

Patients: At screening, patients with COPD (mean age: 64 years) had a mean postbronchodilator percent predicted FEV_1 of 46%, a mean postbronchodilator FEV_1/FVC ratio: 0.48, and a mean mMRC score of 2.4.

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; LAMA=long-acting muscarinic antagonist; LS=least squares; mMRC=modified Medical Research Council.

Designed to help patients with COPD breathe better today

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Advise patients to rinse their mouths with water without swallowing after inhalation.
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following use of ICS, like fluticasone furoate.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.
- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.
- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of ICS in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue TRELEGY and institute alternative therapy.

Please see additional Important Safety Information for TRELEGY throughout.

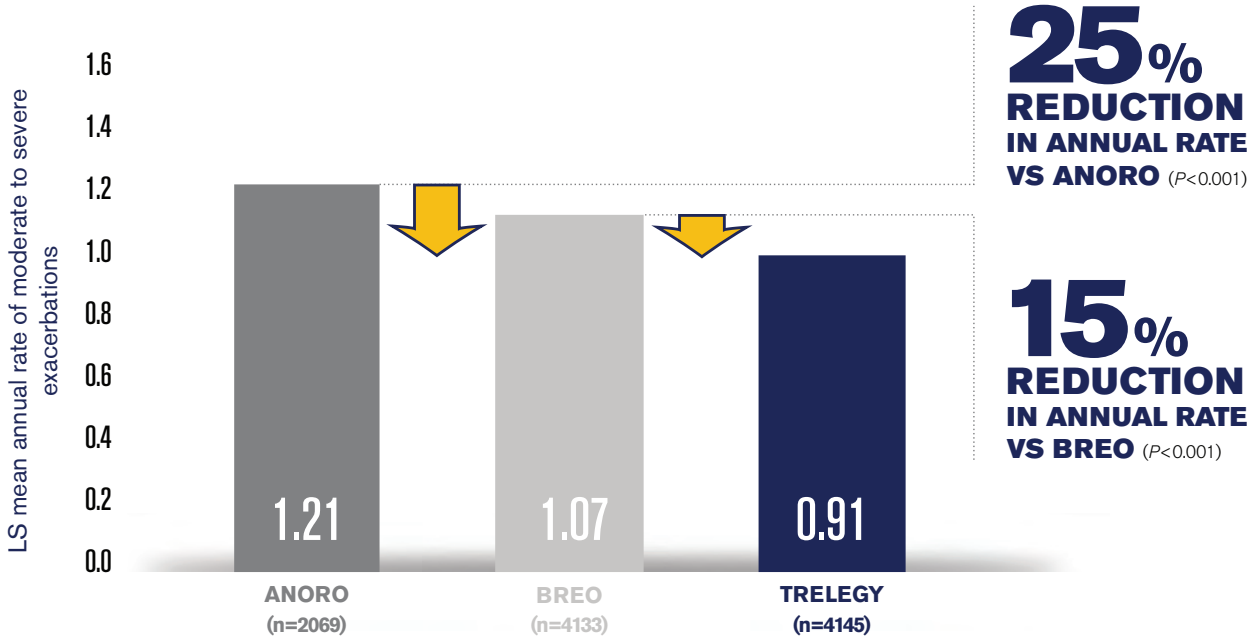
Please see Brief Summary of Prescribing Information for TRELEGY following this ad.

TRELEGY: Helps prevent exacerbations

Superior exacerbation rate reduction vs an ICS/LABA and vs a LAMA/LABA[3]

In patients with a history of COPD exacerbations

PRIMARY ENDPOINT: ANNUAL RATE OF MODERATE TO SEVERE EXACERBATIONS[3]



25% REDUCTION IN ANNUAL RATE VS ANORO (*P*<0.001)

15% REDUCTION IN ANNUAL RATE VS BREO (*P*<0.001)

Request samples or savings coupons for your eligible patients in 3 easy steps. Visit **TRELEGYOffers.com** or scan this code.

IMPACT STUDY DESCRIPTION[2,3]

Design: A 12-month, randomized, double-blind, parallel-group study comparing the rate of moderate to severe exacerbations between TRELEGY and BREO 100/25, an ICS/LABA, and between TRELEGY and ANORO 62.5/25, a LAMA/LABA. Patients were eligible if they were symptomatic with a postbronchodilator percent predicted FEV_1 <50% and a history of 1 or more moderate or severe exacerbations within the previous year, or with a postbronchodilator percent predicted FEV_1 of 50% to 80% and a history of 2 or more moderate exacerbations or 1 severe exacerbation in the previous year.

Patients: At screening, patients with COPD (N=10,355, mean age: 65 years) had a mean postbronchodilator percent predicted FEV_1 of 45.5% and a mean postbronchodilator FEV_1/FVC ratio: 0.47. Patients were randomized (2:2:1) to treatment following a 2-week run-in period on their current COPD treatment. Current medications included ICS + LABA + LAMA (34%), ICS + LABA (26%), LAMA + LABA (8%), LAMA (7%), and other (25%).

Exacerbation severity criteria: Moderate if treatment with systemic corticosteroids and/or antibiotics was required and severe if hospitalization was required.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur.

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

TODAY. TOMORROW. TRELEGY.

Request samples or savings coupons for your eligible patients in 3 easy steps. Visit **TRELEGYOffers.com** or scan this code.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density have been observed with long-term administration of products containing ICS. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of ICS or inhaled anticholinergics. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRELEGY long term.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo + FF/VI) reported in two 12-week clinical trials with UMEC + FF/VI, the components of TRELEGY, (and placebo + FF/VI) were: headache, 4% (3%); back pain, 4% (2%); dysgeusia, 2% (<1%); diarrhea, 2% (<1%); cough, 1% (<1%); oropharyngeal pain, 1% (0%); and gastroenteritis, 1% (0%).
- Additional adverse reactions (≥1% incidence) reported in subjects taking TRELEGY in a 52-week trial included upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

DRUG INTERACTIONS

- TRELEGY should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution, as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of TRELEGY with other anticholinergic-containing drugs, as this may lead to an increase in anticholinergic adverse effects.

USE IN SPECIFIC POPULATIONS

- Use TRELEGY with caution in patients with moderate or severe hepatic impairment, as fluticasone furoate systemic exposure may increase by up to 3-fold. Monitor for corticosteroid-related side effects.

Please see additional Important Safety Information for TRELEGY throughout.

Please see Brief Summary of full Prescribing Information for TRELEGY following this ad.

References: 1. Siler TM, Kerwin E, Sousa A, et al. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies. *Respir Med.* 2015;109(9):1155-1163. **2.** Data on file, GSK. **3.** Lipson DA, Barnhart F, Brealey N, et al; for the IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med.* 2018;378(18):1671-1680.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

FVUJRNA190006 August 2019
Produced in USA.

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

TODAY. TOMORROW. TRELEGY.

BRIEF SUMMARY

TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

TRELEGY is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Important Limitations of Use

TRELEGY is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of TRELEGY is contraindicated in the following conditions: severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

The safety and efficacy of TRELEGY in patients with asthma have not been established. TRELEGY is not indicated for the treatment of asthma.

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

Available data from clinical trials in subjects with COPD do not suggest an increased risk of death with use of LABA in patients with COPD.

5.2 Deterioration of Disease and Acute Episodes

TRELEGY should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. TRELEGY has not been studied in subjects with acutely deteriorating COPD. The initiation of TRELEGY in this setting is not appropriate.

TRELEGY should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. TRELEGY has not been studied in the relief of acute symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with TRELEGY, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If TRELEGY no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of TRELEGY beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of TRELEGY and Use With Other Long-acting Beta$_2$-agonists

TRELEGY should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using TRELEGY should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with TRELEGY. When such an infection develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while treatment with TRELEGY continues, but at times therapy with TRELEGY may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In two 12-week studies of subjects with COPD (N=824), the incidence of pneumonia was <1% for both treatment arms: umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg. Fatal pneumonia occurred in 1 subject receiving placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg.

In a 52-week trial of subjects with COPD (N=10,355), the incidence of pneumonia was 8% for TRELEGY (n=4,151), 7% for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 5% for umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Fatal pneumonia occurred in 12 of 4,151 patients (0.35 per 100 patient-years) receiving TRELEGY, 5 of 4,134 patients (0.17 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (0.29 per 100 patient-years) receiving umeclidinium/vilanterol.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 9 subjects receiving placebo, 10 subjects receiving fluticasone furoate 100 mcg, and 6 subjects receiving vilanterol 25 mcg (<0.2 per 100 patient-years for each treatment group).

5.6 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis), or other conditions associated with severe electrolyte loss. Although TRELEGY may control COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRELEGY. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with TRELEGY. Lung function (forced expiratory volume in 1 second [FEV_1]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to TRELEGY may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (eg, rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (eg, joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate

Continued on next page

on the HPA axis are not observed with the therapeutic doses of fluticasone furoate in TRELEGY. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with TRELEGY should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, appropriate therapy should be considered.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.10 Paradoxical Bronchospasm

As with other inhaled medicines, TRELEGY can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with TRELEGY, it should be treated immediately with an inhaled, short-acting bronchodilator; TRELEGY should be discontinued immediately; and alternative therapy should be instituted.

5.11 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY *[see Contraindications (4)]*.

5.12 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown *[see Clinical Pharmacology (12.2) of full prescribing information]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

TRELEGY, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

In a 52-week trial of subjects with COPD, the exposure-adjusted rates for any on-treatment major adverse cardiac event, including non-fatal central nervous system hemorrhages and cerebrovascular conditions, non-fatal myocardial infarction (MI), non-fatal acute MI, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per 100 patient-years for TRELEGY (n=4,151), 1.9 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 2.2 per 100 patient-years for umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Adjudicated on-treatment deaths due to cardiovascular events occurred in 20 of 4,151 patients (0.54 per 100 patient-years) receiving TRELEGY, 27 of 4,134 patients (0.78 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 16 of 2,070 patients (0.94 per 100 patient-years) receiving umeclidinium/vilanterol.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of adjudicated cardiovascular events (composite of myocardial infarction, stroke, unstable angina, transient ischemic attack, or on-treatment death due to cardiovascular events) was 2.5 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 2.7 for placebo, 2.4 for fluticasone furoate 100 mcg, and 2.6 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to cardiovascular events occurred in 82 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 86 subjects receiving placebo, 80 subjects receiving fluticasone furoate 100 mcg, and 90 subjects receiving vilanterol 25 mcg (annualized incidence rate ranged from 1.2 to 1.3 per 100 patient-years for the treatment groups).

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating TRELEGY and periodically thereafter. If significant reductions in BMD are seen and TRELEGY is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. TRELEGY should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (eg, eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRELEGY long term.

5.15 Worsening of Urinary Retention

TRELEGY, like all medicines containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.

5.16 Coexisting Conditions

TRELEGY, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.17 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1)]*
- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10)]*
- Cardiovascular effects *[see Warnings and Precautions (5.12)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.14)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TRELEGY is based on the safety data from two 12-week treatment trials with the coadministration of umeclidinium and the fixed-dose combination fluticasone furoate/vilanterol and a 52-week long-term trial of TRELEGY compared with the fixed-dose combinations of fluticasone furoate/vilanterol and umeclidinium/vilanterol *[see Clinical Studies (14)]*.

Trials 1 and 2

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umeclidinium + fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol. A total of 824 subjects with COPD across two 12-week, randomized, double-blind clinical trials received at least 1 dose of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg administered once daily (mean age: 64 years; 92% white, 66% male across all treatments) *[see Clinical Studies (14) of full prescribing information]*. The incidence of adverse reactions associated with the use of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg presented in Table 1 is based on the two 12-week trials.

Table 1. Adverse Reactions With Umeclidinium + Fluticasone Furoate/Vilanterol With ≥1% Incidence and More Common

Continued on next page

Than Placebo + Fluticasone Furoate/Vilanterol (Trials 1 and 2)

Adverse Reaction	Umeclidinium + Fluticasone Furoate/ Vilanterol (n=412) %	Placebo + Fluticasone Furoate/ Vilanterol (n=412) %
Nervous system disorders		
Headache	4	3
Dysgeusia	2	<1
Musculoskeletal and connective tissue disorders		
Back pain	4	2
Respiratory, thoracic, and mediastinal disorders		
Cough	1	<1
Oropharyngeal pain	1	0
Gastrointestinal disorders		
Diarrhea	2	<1
Infections and infestations		
Gastroenteritis	1	0

Trial 3 - Long-term Safety Data

A 52-week trial (Trial 3) evaluated the long-term safety of TRELEGY compared with the fixed-dose combinations of fluticasone furoate/vilanterol 100 mcg/25 mcg and umeclidinium/vilanterol 62.5 mcg/25 mcg. A total of 10,355 subjects with COPD with a history of moderate or severe exacerbations within the prior 12 months were randomized (2:2:1) to receive TRELEGY, fluticasone furoate/vilanterol, or umeclidinium/vilanterol administered once daily in a double-blind clinical trial (mean age: 65 years, 77% white, 66% male across all treatments) *[see Clinical Studies (14)]*.

The incidence of adverse reactions in the long-term trial were consistent with those in Trials 1 and 2. However, in addition to the adverse reactions shown in Table 1, adverse reactions occurring in ≥1% of the subjects treated with TRELEGY (n=4,151) for up to 52 weeks also included upper respiratory tract infection, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, oral candidiasis *[see Warnings and Precautions (5.4)]*, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of TRELEGY with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.14, 5.15)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of TRELEGY or its individual components, fluticasone furoate, umeclidinium, and vilanterol, in pregnant women to inform a drug-associated risk.

Clinical Considerations

Labor and Delivery: TRELEGY should be used during late gestation and labor only if the potential benefit justifies the potential for risks related to beta-agonists interfering with uterine contractility.

8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRELEGY and any potential adverse effects on the breastfed child from fluticasone furoate, umeclidinium, or vilanterol, or from the underlying maternal condition.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of TRELEGY in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. In Trial 3, 2,265 subjects aged 65 years and older, of which 565 subjects were aged 75 years and older, were administered TRELEGY. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

TRELEGY has not been studied in subjects with hepatic impairment. Information on the individual components is provided below.

Fluticasone Furoate/Vilanterol

Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

Umeclidinium

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls.

Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No human overdosage data has been reported for TRELEGY.

TRELEGY contains fluticasone furoate, umeclidinium, and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to TRELEGY. Treatment of overdosage consists of discontinuation of TRELEGY together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Fluticasone Furoate

Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*.

Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1000 mcg of umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.3 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use *of full prescribing information*).

Not for Acute Symptoms

Inform patients that TRELEGY is not meant to relieve acute symptoms of COPD, and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Continued on next page

BRIEF SUMMARY

TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation *(cont'd)*

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with TRELEGY without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other LABA.

Local Effects

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (ie, oral) antifungal therapy while still continuing therapy with TRELEGY, but at times therapy with TRELEGY may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression

Advise patients that TRELEGY may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to TRELEGY.

Paradoxical Bronchospasm

As with other inhaled medicines, TRELEGY can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue TRELEGY and contact their healthcare provider right away.

Hypersensitivity Reactions, Including Anaphylaxis

Advise patients that hypersensitivity reactions (eg, anaphylaxis, angioedema, rash, urticaria) may occur after administration of TRELEGY. Instruct patients to discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Glaucoma and Cataracts

Advise patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (eg, eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develop.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develop.

Risks Associated With Beta-agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 08/2019 TRL:5BRS

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TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

Environmental scan: Drivers of social, political, and environmental change

BY THERESE BORDEN
MDedge News

We are living through an era of rapidly accelerated social, political, and environmental change. Spiraling costs of medical care, consumer activism around health care delivery, an aging population, and growing evidence of climate change are just some of the big currents of change. These trends are national and global in scope, and as such, far beyond any one profession or sector to shape or control. It remains for the medical profession to understand the currents of the time and adapt in order to thrive in the future.

David A. Schulman, MD, FCCP, Professor of Medicine at Emory University School of Medicine, Atlanta, has reflected on these trends of the times and their impact on chest physicians. He commented, "In 1957, the American Medical Association adopted the Principles of Medical Ethics, which noted that 'the responsibilities of the physician extend not only to the individual, but also to society where these responsibilities deserve his [her] interest and participation in activities which have the purpose of improving both the health and the well-being of the individual and the community.'[1] While this terminology has evolved in more recent iterations of the Code of Medical Ethics, it is more important than ever for physicians to be cognizant of the effects of social, political, and environmental factors on personal and public health. These external pressures seem to be growing in a climate where the country is more polarized than ever, and conversations on some of these topics can introduce unnecessary tension on interpersonal relationships, but there are still many things in this domain on which we can all agree."

CHEST® INSPIRATION: Pacing the Future

Two trends of particular interest to chest physicians are the potential impact of climate change on patients, and the "greying" of the patient population. Both are likely to have a significant impact on medical practice in the decades to come.

Patients will feel climate change

Environmental factors affecting the air we breathe are of primary concern for patients with a broad range of cardiorespiratory conditions.[2] Healthy but vulnerable infants, children, pregnant women, and the elderly may also feel the effects.[3] Air pollution, increased levels of pollen and ground-level ozone, and wildfire smoke are all tied to climate change and all can have a direct impact on the patients seen by chest physicians. Individuals exposed to these environmental conditions may experience diminished lung function, resulting in increased hospital admissions. Keeping up with the latest research on probable health impacts of these environmental trends will be on the agenda of most chest physicians.[4] Professional societies will need to provide for the educational needs of members, as the field will respond with new diagnostic tools and treatments.

Dr. Schulman said, "Stresses on our physical environment are affecting our patients. Environmental warming may increase the spread of mosquito-borne illnesses.[5] The lack of available clean water in many areas of the world will increase the risk of water-borne infections. Higher levels of pollution will lead to poorer air quality and an increased risk of respiratory infections, exacerbations of respiratory disease, loss of lung function, and the eventual development of lung cancer. While any one of us may not be able to make a change on a global level, we do bear a responsibility to ensure that our patients are cognizant of the effects of environmental exposures on their health, and how these effects can be mitigated (which may include minimizing time outside on days with poor air quality and implementing methods to improve indoor air quality)."


Dr. Schulman

Mind the generation gap

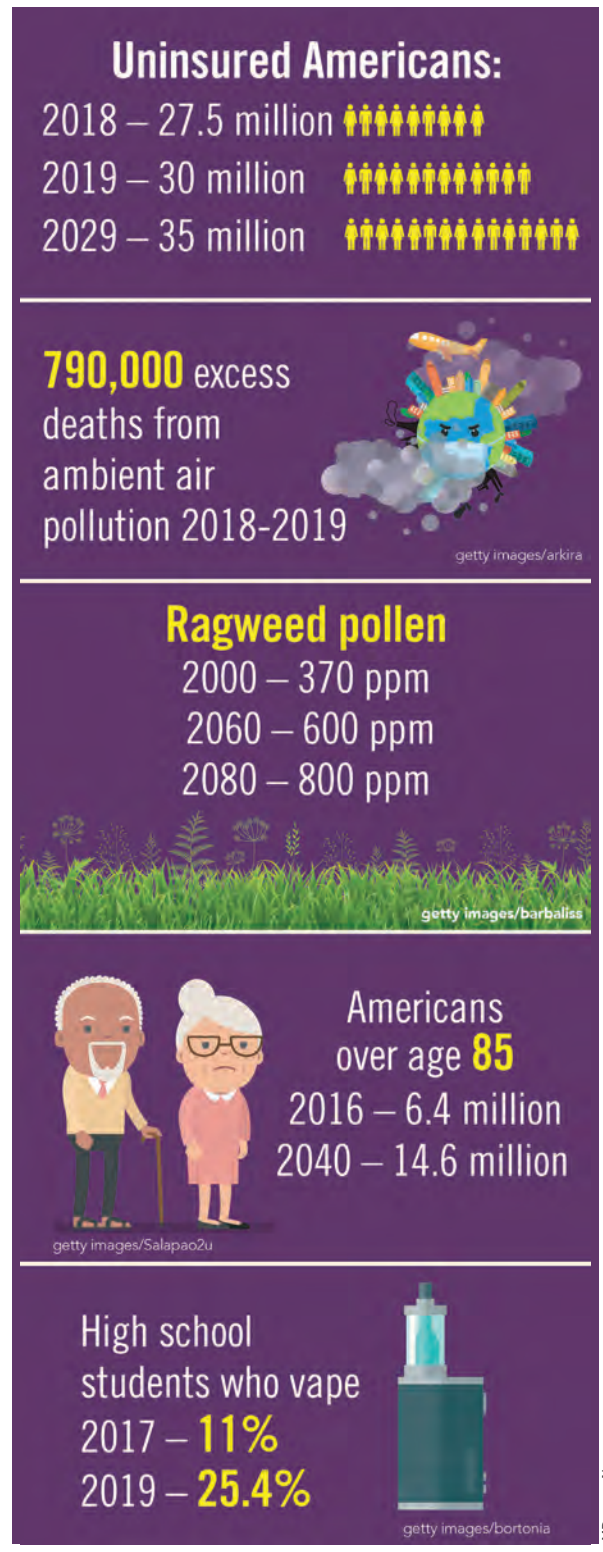
The population in the United States is primarily under age 65 (84%), but the number of older citizens is on the rise. In 2016, there were 49.2 million people age 65 or older, and this number is projected to almost double to 98 million in 2060. The 85 and over population is projected to more than double from 6.4 million in 2016 to 14.6 million in 2040 (a 129% increase).[6]

The medical needs of the aging population are already part of most medical institutions' planning, but the current uncertainty in the health insurance market and the potential changes in Medicare coverage, not to mention the well-documented upcoming physician shortage,[7] are complicating the planning process. Almost all acknowledge the "greying" of the population, but current approaches may not be sufficient given the projected scale of the problems. This includes major increases in patients with chronic illnesses and the need for upscaling long-term geriatric care.

Dr. Schulman notes that there will likely be "a workforce shortage, unless we make deliberate efforts to increase the workforce. More aggressive recruitment of individuals into the health-care industry, including those traditionally under-represented in medicine, will be an important component of this endeavor. Mitigating burnout, which impacts both provider efficiency and leads to early exit from the practice of medicine, will be another critical step in this process."

In addition to the problem of planning for treating a growing elderly population, several concerning trends are appearing among younger groups. E-cigarette use among middle- and high-school students may create millions of future patients with lung damage and nicotine addictions.[8] Government intervention in this smoking epidemic is lagging behind the rapid spread of this unhealthy habit among young people.[9] Dr. Schulman is concerned about new sources of tobacco delivery to young people. "Independent of the recent spate of vaping-associated pulmonary injury, the increasing use of nicotine-delivery systems by our youth is highly troubling. In much the same way that we have long advised our tobacco-abusing patients to minimize or discontinue smoking, health-care providers need to aggressively screen for (and advocate against) the use of alternative methods of nicotine delivery, at least until such time that one of them is proven to be safe in long-term studies."

Continued on page 61



FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.
FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

NOW AVAILABLE

At-home administration with FASENRA Pen

At-home administration with FASENRA Pen

In-office administration with the prefilled syringe

FASENRA is the only respiratory biologic that combines Q8W dosing with at-home and in-office administration options[1]

Dosing comparisons do not imply comparable efficacy, safety, or FDA-approved indications.

FASENRA is for subcutaneous use only. The recommended dose of **FASENRA** is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter.

FASENRA is intended for use under the guidance of a healthcare professional to ensure appropriate initiation and follow-up of patients. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended.

Administer **FASENRA** into the thigh or abdomen. The upper arm can also be used if a healthcare professional or caregiver administers the injection.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction.

Acute Asthma Symptoms or Deteriorating Disease
FASENRA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection
It is unknown if FASENRA will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until infection resolves.

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥ 5%) include headache and pharyngitis.

Injection site reactions (eg, pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Scan the QR code or visit FASENRAhcp.com to learn more

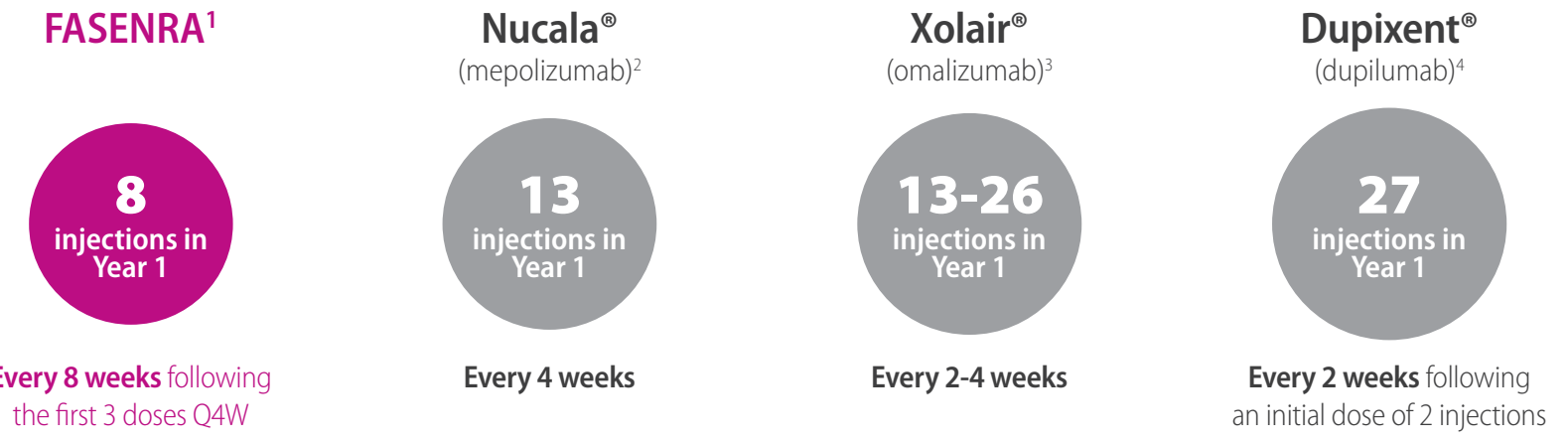
Please see additional Important Safety Information on back and Brief Summary of full Prescribing Information on adjacent page.

Fasenra® (benralizumab) Subcutaneous Injection 30 mg | Fasenra Pen™ (benralizumab) Subcutaneous Injection 30 mg

FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.
FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

FASENRA is the only respiratory biologic that combines Q8W dosing with at-home and in-office administration options[1]

FASENRA offers patients the fewest injections per year



Dosing comparisons do not imply comparable efficacy, safety, or FDA-approved indications.

- **FASENRA** is for subcutaneous use only. The recommended dose of **FASENRA** is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter[1]
- **FASENRA** is intended for use under the guidance of a healthcare professional to ensure appropriate initiation and follow-up of patients. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended[1]
- **FASENRA** Pen is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare professional determines it is appropriate. Administer **FASENRA** into the thigh or abdomen. The upper arm can also be used if a healthcare professional or caregiver administers the injection[1]
- Prior to administration, warm **FASENRA** by leaving carton at room temperature for about 30 minutes. **FASENRA** may be left out of the refrigerator at room temperature for up to 14 days in the original carton[1]
- Administer **FASENRA** within 14 days of removing from the refrigerator or discard into sharps container[1]

Talk to your patients about the most convenient administration option for them

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothertobaby.org/fasenra.

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

INDICATION

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.
- FASENRA is not indicated for treatment of other eosinophilic conditions
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus

References: 1. FASENRA [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019. **2.** Nucala [package insert]. Research Triangle Park, NC: GlaxoSmithKline LLC; September 2019. **3.** Xolair [package insert]. South San Francisco, CA: Genentech Inc; May 2019. **4.** Dupixent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. and sanofi-aventis U.S. LLC; June 2019.

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

Please see additional Important Safety Information on front and adjacent Brief Summary of full Prescribing Information.

Fasenra® (benralizumab) Subcutaneous Injection 30 mg | Fasenra Pen™ (benralizumab) Subcutaneous Injection 30 mg

FASENRA® (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

General Administration Instructions

FASENRA is intended for use under the guidance of a healthcare provider. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Administer FASENRA into the thigh or abdomen. The upper arm can also be used if a healthcare provider or caregiver administers the injection. Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter.

Prefilled Syringe

The prefilled syringe is for administration by a healthcare provider.

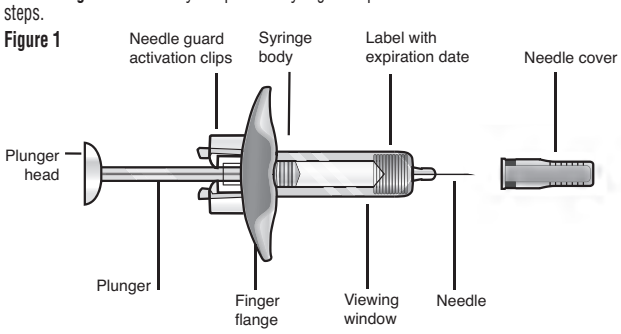
Autoinjector (FASENRA PEN™)

FASENRA PEN is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare provider determines it is appropriate.

Instructions for Administration of FASENRA Prefilled Syringe (Healthcare Providers)

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

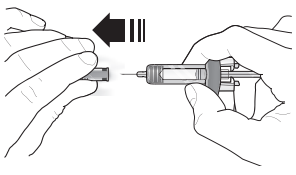
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

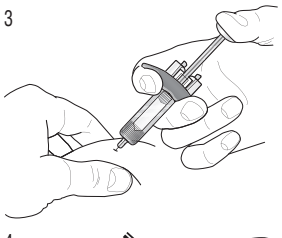
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. The syringe may contain small air bubbles; this is normal. **Do not** expel the air bubbles prior to administration.

2



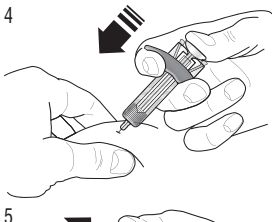
Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3



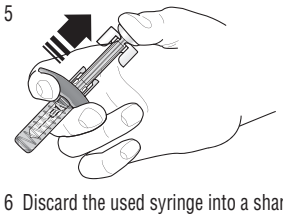
Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4



Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5



After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

Instructions for Administration of FASENRA PEN

Refer to the FASENRA PEN 'Instructions for Use' for more detailed instructions on the preparation and administration of FASENRA PEN *[See Instructions for Use in the full Prescribing Information]*. A patient may self-inject or the patient caregiver may administer FASENRA PEN subcutaneously after the healthcare provider determines it is appropriate.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued *[see Contraindications (4) in the full Prescribing Information]*.

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14) in the full Prescribing Information]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two Phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n=841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n=822), and placebo (n=847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1) in the full Prescribing Information]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N=822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions†	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

† Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n=73) or placebo (n=75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14) in the full Prescribing Information]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post approval use of FASENRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to FASENRA or a combination of these factors.

Immune System Disorders: Hypersensitivity reactions, including anaphylaxis.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting mothertobaby.org/Fasenra.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see *Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n=320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use for FASENRA PEN) before the patient starts using FASENRA and each time the prescription is renewed as there may be new information they need to know.

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique using the FASENRA PEN, including aseptic technique, and the preparation and administration of FASENRA PEN prior to use. Advise patients to follow sharps disposal recommendations [*see Instructions for Use in the full Prescribing Information*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare provider if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting mothertobaby.org/Fasenra *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Manufactured by
AstraZeneca AB
Södertälje, Sweden SE-15185
US License No. 2059

Distributed by
AstraZeneca Pharmaceuticals LP,
Wilmington, DE 19850

Rev. 10/19 US-30661 10/19

How to carve out a career as an educator during fellowship

BY JUSTIN K. LUI, MD

Editor's Note - As CHEST has just awarded the designation of Distinguished CHEST Educator (DCE) to 173 honorees at CHEST 2019 in New Orleans, this blog reminds fellows to start early to pursue a clinician educator role throughout their career.

While fellowship training is a time to continue building the foundation of expert clinical knowledge, it also offers an opportunity to start assembling a portfolio as a clinician educator. It takes time to compile educational scholarship and to establish a reputation within the communities of both teachers and learners, so it pays to get a head start. Moreover, it also takes time to master techniques for effective teaching to become that outstanding educator that you once looked up to as a medical student or resident. Below are some things that I found helpful in jump-starting that path during fellowship training.

Find a capable mentor

As with any sort of career planning, mentorship is key. Mentorship can open doors to expand your network and introduce opportunities for scholarship activities. Find a mentor who shares similar views and values with something that you feel passionate about. If you are planning on starting a scholarly project, make sure that your mentor has the background suited to help you maximize the experience and offer you the tools needed to achieve that end.

Determine what you are passionate about

Medical education is a vast field. Try to find something in medical education that is meaningful to you, whether it be in undergraduate medical education or graduate medical education or something else altogether. You want to be able to set yourself up for success, so the work has to be worthwhile.

If you are planning on starting a scholarly project, make sure that your mentor has the background suited to help you maximize the experience and offer you the tools needed to achieve that end.

Seek out opportunities to teach

There are always opportunities to teach whether it entails precepting medical students on patient interviews or going over pulmonary/critical care topics at resident noon conferences. What I have found is that active participation in teaching opportunities tends to open a cascade of doors to more teaching opportunities.

Look for opportunities to be involved in educational committees

Medical education, much like medicine, is a highly changing field. Leadership in medical education is always looking for resident/fellow representatives to bring new life and perspective to educational initiatives. Most of these opportunities do not require too much of a time commitment, and most committees often meet on a once-monthly basis. However, it connects you with faculty who are part of the leadership who can guide and help set you up for future success in medical education. During residency, I was able to take part in the intern curriculum committee to advise the direction of intern report. Now as a fellow, I've been able to meet many faculty and fellows with similar interests as mine in the *CHEST* Trainee Work Group.

Engage in scholarly activities

It is one thing to have a portfolio detailing teaching experiences, but it is another thing to have demonstrated published works in the space of medical education. It shows long-term promise as a clinician educator, and it shows leadership potential in advancing the field. It doesn't take much to produce publications in medical education—there are always journals who look for trainees to contribute to the field whether it be an editorial or systematic review or innovative ideas.

About the author

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Reprinted from CHEST's Thought Leader's Blog, July 2019. This post is part of Our Life as a Fellow blog post series and includes "fellow life lessons" from current trainees in leadership with CHEST.

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In 2019, health coverage for adults has started to decline again after a decade of gains,[10] so the possibility of this becoming a long-term trend has to be considered in planning for the treatment of the young population as they enter adulthood.[11]

Final thoughts

Some issues, including the increase in tobacco usage and aging patients with more complex problems, are likely to be addressed through both continuing education and guidelines/standards. On the other hand, with a growing population of individuals under 30, we can expect increasing unrest with the status quo, a demand for change in public policy, and a higher adoption of new models for the diagnosis, treatment, and ongoing care of health-related issues.

In order to have a real impact, organizations will need to explore new partnerships for addressing issues related to climate change and the increase in tobacco use by minors. Members need to stay up-to-date using information curated and shared by trusted organizations and sources.

Note: Background research performed by Avenue M Group.

CHEST Inspiration is a collection of programmatic initiatives developed by the American College of Chest Physicians leadership and aimed at stimulating and encouraging innovation within the association. One of the components of CHEST Inspiration is the Environmental Scan, a series of articles focusing on the internal and external environmental factors that bear on success currently and in the future. See "Envisioning the Future: The CHEST Environmental Scan," CHEST Physician, June 2019, p. 44, for an introduction to the series.

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SLEEP STRATEGIES

CPAP vs noninvasive ventilation for obesity hypoventilation syndrome

BY NARESH A. DEWAN MD, FCCP

The conventional approach to treat hypoventilation has been to use noninvasive ventilation (NIV), while continuous positive airway pressure (CPAP) that does not augment alveolar ventilation improves gas exchange by maintaining upper airway patency and increasing functional residual capacity. Why, then, are we debating the use of CPAP vs NIV in the treatment of obesity hypoventilation syndrome (OHS)? To understand this rationale, it is important to first review the pathophysiology of OHS. The hallmark of OHS is resting daytime awake arterial $PaCO_2$ of 45 mm Hg or greater in an obese patient (BMI > 30 kg/m^2) in absence of any other identifiable cause. To recognize why only some but not all obese subjects develop OHS, it is important to understand the different components of pathophysiology that contribute to hypoventilation: (1) obesity-related reduction in functional residual capacity and lung compliance with resultant increase in work of breathing; (2) central hypoventilation related to leptin resistance and reduction in respiratory drive with REM hypoventilation; and (3) upper airway obstruction caused by upper airway fat deposition along with low FRC contributing to pharyngeal airway narrowing and increased airway collapsibility (Masa JF, et al. *Eur Respir Rev.* 2019; 28:180097).

Dr. Dewan

CPAP vs NIV for OHS

Let us examine some of the studies that have compared the short-term efficacy of CPAP vs NIV in patients with OHS. In a small randomized controlled trial (RCT), the effectiveness of CPAP and NIV was compared in 36 patients with OHS (Piper AJ, et al. *Thorax.* 2008;63:395). Reduction in $PaCO_2$ at 3 months was similar between the two groups. However, patients with persistent nocturnal desaturation despite optimal CPAP were excluded from the study. In another RCT of 60 patients with OHS who were either in stable condition or after an episode of acute on chronic hypercapnic respiratory failure, the use of CPAP or NIV showed similar improvements at 3 months in daytime $PaCO_2$, quality of life, and sleep parameters (Howard ME, et al. *Thorax.* 2017;72:437).

In one of the largest randomized control trials, the Spanish Pickwick study randomized 221 patients with OHS and AHI >30/h to NIV, CPAP, and lifestyle modification (Masa JF, et al. *Am J Respir Crit Care Med.* 2015:192:86). PAP therapy included NIV that consisted of in-lab titration with bilevel PAP therapy targeted to tidal volume 5-6 mL/kg of actual body weight or CPAP. Lifestyle modification served as the control group. Primary outcome was the change in $PaCO_2$ at 2 months. Secondary outcomes were symptoms, HRQOL, polysomnographic parameters, spirometry, and 6-min walk distance (6 MWD). Mean AHI was 69/h, and mean PAP settings for NIV and CPAP were 20/7.7 cm and 11 cm H_2O, respectively. NIV provided the greatest improvement in $PaCO_2$ and serum HCO_3 as compared with control group but not relative to CPAP group. CPAP improved $PaCO_2$ as compared with control group only after adjustment of PAP use. Spirometry and 6 MWD and some HRQOL measures improved slightly more with NIV as compared with CPAP. Improvement in symptoms and polysomnographic parameters was similar between the two groups.

In another related study by the same group (Masa JF, et al. *Thorax.* 2016;71:899), 86 patients with OHS and mild OSA (AHI <30/h), were randomized to NIV and lifestyle modification. Mean AHI was 14/h and mean baseline $PaCO_2$ was 49 +/-4 mm Hg. The NIV group with mean PAP adherence at 6 hours showed greater improvement in $PaCO_2$ as compared with lifestyle modification (6 mm vs 2.8 mm Hg). They concluded that NIV was better than lifestyle modification in patients with OHS and mild OSA.

To determine the long-term clinical effectiveness of CPAP vs NIV, patients in the Pickwick study, who were initially assigned to either CPAP or NIV treatment group, were continued on their respective treatments, while subjects in the control group were again randomized at 2 months to either CPAP or NIV (Masa JF, et al. *Lancet.* 2019;393:1721). All subjects (CPAP n=107; NIV n=97) were followed for a minimum of 3 years. CPAP and NIV settings (pressure-targeted to desired tidal volume) were determined by in-lab titration without transcutaneous CO_2 monitor, and daytime adjustment of PAP to improve oxygen saturation. Primary outcome was the number of hospitalization days per year. Mean CPAP was 10.7 cm H_2O pressure and NIV 19.7/8.18 cm H_2O pressure with an average respiratory rate of 14/min. Median PAP use and adherence > 4 h, respectively, were similar between the two groups (CPAP 6.0 h, adherence > 4 h 67% vs NIV 6.0/h, adherence >4 h 61%). Median duration of follow-up was 5.44 years (IOR 4.45-6.37 years) for both groups. Mean hospitalization days per patient-year were similar be-

The hallmark of OHS is resting daytime awake arterial $PaCO_2$ of 45 mm Hg or greater in an obese patient (BMI > 30 kg/m^2) in absence of any other identifiable cause.

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Meet the new *CHEST*® journal Deputy Editors

Christopher L. Carroll, MD, MS, FCCP
Dr. Carroll is a pediatric critical care physician at Connecticut Children's Medical Center and a Professor of Pediatrics at the University of Connecticut. Dr. Carroll has a long-standing interest in social media and its use in academic medicine and medical education. He was an early adopter of social media in pulmonary and critical care medicine,and researches the use of social media in academic medicine. Dr. Carroll has served on numerous committees within CHEST, including most recently as Trustee of the CHEST Foundation and Chair of the Critical Care NetWork. Before being appointed Deputy Editor for Web and Multimedia for the journal *CHEST,* Dr. Carroll served as Social Media Section Editor from 2012-2018, and then Web and Multimedia Editor for the journal. He also co-chairs the Social Media Workgroup for CHEST. When not working or tweeting, Dr. Carroll can be found camping with his Boy Scout troop and parenting three amazingly nerdy and talented children who are fortunate to take after their grandparents.


Dr. Carroll

Darcy D. Marciniuk, MD, Master FCCP
Dr. Marciniuk is a Professor of Respirology, Critical Care, and Sleep Medicine, and Associate Vice-President Research at the University of Saskatchewan, Saskatoon, SK, Canada. He is recognized internationally as an expert and leader in clinical exercise physiology, COPD, and pulmonary rehabilitation. Dr. Marciniuk is a Past President of CHEST and served as a founding Steering Committee member of Canada's National Lung Health Framework, member and Chair of the Royal College of Physicians and Surgeons of Canada Respirology Examination Board, President of the Canadian Thoracic Society (CTS), and Co-Chair of the 2016 CHEST World Congress and 2005 CHEST Annual Meeting. He was the lead author of three COPD clinical practice guidelines, a panel member of international clinical practice guidelines in COPD, cardiopulmonary exercise testing, and pulmonary rehabilitation, and was a co-author of the published joint Canadian Thoracic Society/CHEST clinical practice guideline on preventing acute exacerbations of COPD.


Dr. Marciniuk

Susan Murin, MD, MSc, MBA, FCCP
Dr. Murin is currently serving as Vice-Dean for Clinical Affairs and Executive Director of the UC Davis Practice Management Group. She previously served as Program Director for the Pulmonary and Critical Care fellowship, Chief of the Division of Pulmonary, Critical Care and Sleep Medicine, and Vice-Chair for Clinical Affairs at UC Davis. Her past national service has included membership on the ACGME's Internal Medicine RRC, Chair of the Pulmonary Medicine test-writing committee for the ABIM, and Chair of the Association of Pulmonary and Critical Care Medicine Program Directors. She has a long history of service to CHEST in a variety of roles and served as an Associate Editor of the *CHEST* journal for 14 years. Dr. Murin's research has been focused in two areas: epidemiology of venous thromboembolism and the effects of smoking on the natural history of breast cancer. She remains active in clinical care and teaching at both UC Davis and the Northern California VA. When not working, she enjoys spending time with her three grown children, scuba diving, and playing tennis.


Dr. Murin

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tween the two groups (CPAP 1.63 vs NIV 1.44 days; adj RR 0.78, 95% CI 0.34-1.77; *P*=0.561). Overall mortality, adverse cardiovascular events, and arterial blood gas parameters were similar between the two groups, suggesting equal efficacy of CPAP and NIV in this group of stable patients with OHS with an AHI >30/h. Given the low complexity and cost of CPAP vs NIV, the authors concluded that CPAP may be the preferred PAP treatment modality until more studies are available.

An accompanying editorial (Murphy PB, et al. *Lancet.* 2019; 393:1674), discussed that since this study was powered for superiority as opposed to noninferiority of NIV (20% reduction in hospitalization with NIV when compared with CPAP), superiority could not be shown, due to the low event rate for hospitalization (NIV 1.44 days vs CPAP 1.63 days). It is also possible optimum NIV titration may not have been determined since TCO_2 was not used. Furthermore, since this study was done only in patients with OHS and AHI >30/h, these results may not be applicable to patients with OHS and low AHI < 30/h who are more likely to have central hypoventilation and comorbidities, and this group may benefit from NIV as compared with CPAP.

Novel modes of bi-level PAP therapy

There are limited data on the use of the new bi-level PAP modalities, such as volume-targeted pressure support ventilation (PS) with fixed or auto-EPAP. The use of intelligent volume-assured pressure support ventilation (iVAPS) vs standard fixed pressure support ventilation in select OHS patients (n=18) showed equivalent control of chronic respiratory failure with no worsening of sleep quality and better PAP adherence (Kelly JL, et al. *Respirology.* 2014;19:596). In another small randomized, double-blind, crossover study, done on two consecutive nights in 11 patients with OHS, the use of auto-adjusting EPAP was noninferior to fixed EPAP (10.8 cm vs 11.8 cm H_2O pressure), with no differences in sleep quality and patient preference (McArdle N. *Sleep*. 2017;40:1). Although the data are limited, these small studies suggest the use of new PAP modalities, such as variable PS to deliver target volumes and auto EPAP could offer the potential to initiate bi-level PAP therapy in outpatients without the in-lab titration. More studies are needed before bi-level PAP therapy can be safely initiated in outpatients with OHS.

Summary

How can we utilize the most effective PAP therapy for patients with OHS? Can we use a phenotype-dependent approach to PAP treatment options? The answer is probably yes. Recently published ATS Clinical Practice Guideline (*Am J Respir Crit Care Med.* 2019;200:e6-e24) suggests the use of PAP therapy for stable ambulatory patients with OHS as compared with no PAP therapy, and patients with OHS with AHI >30/h (approximately 70% of the OHS patients) can be initially started on CPAP instead of NIV. Patients who have persistent nocturnal desaturation despite optimum CPAP can be switched to NIV. On the other hand, data are limited on the use of CPAP in patients with OHS with AHI <30/h, and these patients can be started on NIV. PAP adherence >5-6 h, and weight loss using a multidisciplinary approach should be encouraged for all patients with OHS.

Dr. Dewan is Professor and Program Director, Sleep Medicine; Division of Pulmonary, Critical Care and Sleep Medicine; Chief, Pulmonary Section VA Medical Center; Creighton University, Omaha, Nebraska.

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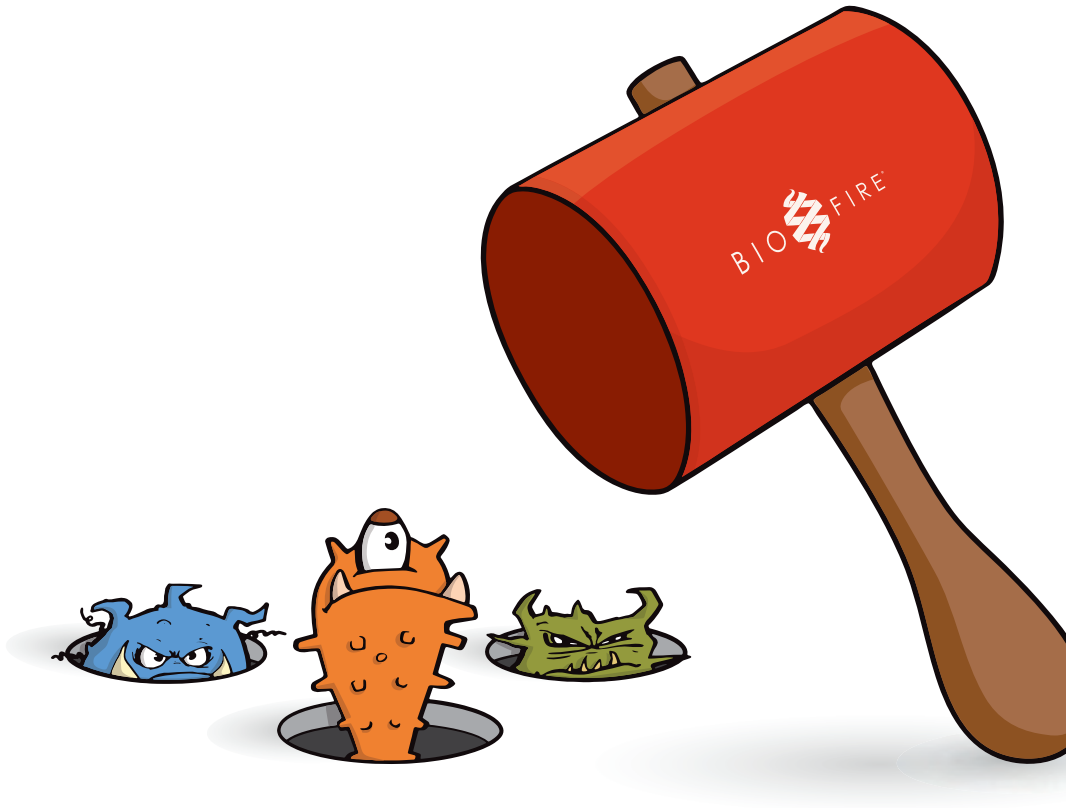

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