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CHEST® Physician

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HAZEMMKAMAL/Getty Images

CDC closing in on source of vaping-associated lung injuries

BY THERESE BORDEN
MDedge News

The Centers for Disease Control and Prevention has announced a possible breakthrough in the hunt for the source of a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injuries (EVALI): vitamin E acetate found in lung fluid of victims.

In a telebriefing, Anne Schuchat, MD, the CDC's principal deputy director, provided an update on recent lab findings and on case and death numbers reported so far to the CDC. The findings and more case information were published in the Mortality and Morbidity Weekly Report.

At the telebriefing, Dr. Schuchat stated that CDC has received 29 samples of bronchoalveolar lavage (BAL) fluid from EVALI patients from 10 states and that vitamin E acetate was identified in all samples. Vitamin E acetate has already been found in some vaping devices and the discovery of the chemical in the lungs of patients increases the likelihood that this toxin is at least one source of EVALI. These findings are the first to link substances found in vaping products with biological samples from patients hospitalized with EVALI.

Tetrahydrocannabinol (THC) was found in 23 of 28 samples tested, and nicotine was found in 16 of 26 samples tested. Other diluents and addi-

VAPING // *continued on page 7*

Cystic fibrosis breakthrough: Triple therapy effective for common mutation

BY STEVE CIMINO
MDedge News

Reinforcing previous findings, a new study has determined that the next-generation corrector elexacaftor, in combination with tezacaftor and ivacaftor, can effectively treat patients with Phe508del–minimal function genotypes who did not respond to previous cystic fibrosis transmembrane conductance regulator (CFTR) modulator regimens.

"These results provide evidence that elexacaftor-tezacaftor-ivacaftor can modulate a single Phe508del allele in people with cystic fibrosis, thus addressing the underlying cause of disease in the large majority of patients," wrote Peter G. Middleton, PhD, of the University of Sydney and his coauthors. The study was published in the New England Journal of Medicine.

To further determine if the elexacaftor -tezacaftor-ivacaftor regimen was effective and safe, the researchers launched a randomized, placebo-controlled phase 3 trial of 403 cystic

CYSTIC FIBROSIS // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST

CHEST Foundation establishes Mark J. Rosen, MD, Master FCCP Endowment.

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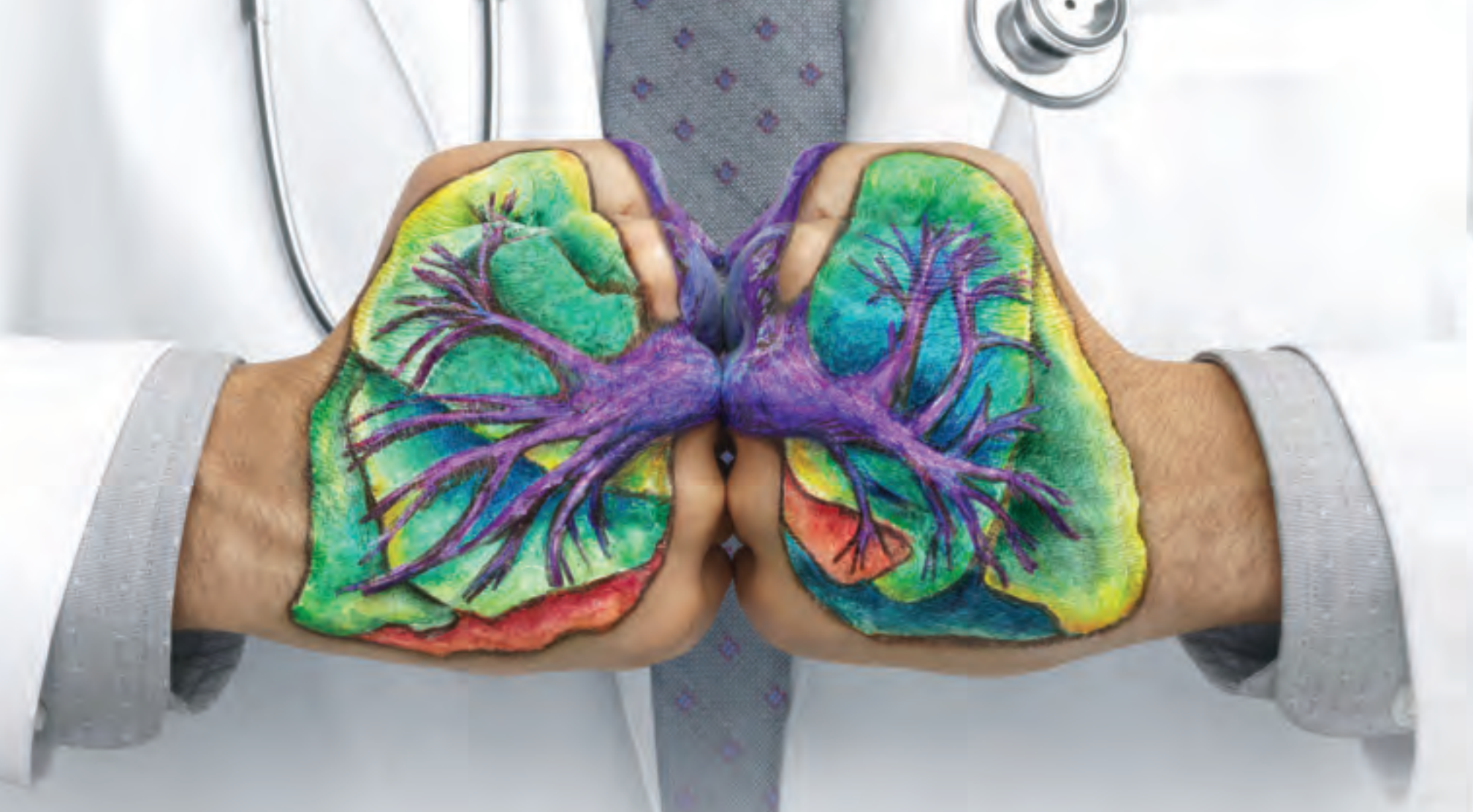

Indication

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

FDA noncommittal on e-cigarette action

BY GREGORY TWACHTMAN
MDedge News

Despite some strong words by the White House in September 2019 regarding action to help curb the growing epidemic of youth vaping and e-cigarette use, a Food and Drug Administration official deflected questions on when the agency would act and what actions it was planning on taking.

"I was actually shocked that, in a hearing that is focused in part on the youth vaping epidemic [that] your testimony, both written and oral here, made no mention of the administration's Sept. 11 announcement that it intended to clear the market of all unauthorized non–tobacco-flavored vaping products," said Sen.Patty Murray (D-Wash.), ranking member of the Senate Health, Education, Labor and Pen-

sions Committee, during a Nov. 13 hearing to Mitchell Zeller, director of the FDA's Center for Tobacco Products. "Why is that not included in your testimony?"

Director Zeller would only offer a vague response, testifying that the agency is "committed to doing everything that we can to prevent kids from using any tobacco product, including e-cigarettes, and that we are continuing to develop a policy approach that aligns with that concern."

When Sen. Murray pressed further, Director Zeller deflected: "I think that any questions that the committee has about the announcement that the White House and anything related to what remains a deliberative process on policy is best referred to the White House itself."

He would not even offer any perspective on when the FDA might take actual regulatory action when asked about it by Sen. Murray.

"I can't give you a specific timeline, Senator, other than to say that the deliberative process continues," Director Zeller responded, telling her that "I really would refer you and the committee to the White House to ask specific questions about where we are."

The hearing, called to examine the response to lung illnesses and rising youth e-cigarette usage, shed no new light on the issue. And while Director Zeller outlined the numerous educational campaigns being aimed at convincing youth to not use e-cigarettes, Committee Chairman Lamar Alexander (R-Tenn.) questioned whether the FDA was doing an adequate job.

Mitchell Zeller, director of the FDA's Center for Tobacco Products, deflected questions on when the agency would act on curbing e-cigarette use among youth, and said, "I really would refer you and the committee to the White House to ask specific questions about where we are."

The FDA, from late 2017 to the end of 2020, "will wind up investing about $150 million in a massive, multimedia public education campaign to get the word out to kids" on the dangers of vaping, Director Zeller said, adding that the agency is "aggressively enforcing" youth access restrictions in targeting sellers of e-cigarette products to minors.

"Well, obviously we are not making much progress with youth use ... if one in four of American high schoolers, according to your statistics, are using e-cigarettes," Sen. Alexander said.

While most on the committee were focused on the rising numbers of youth vaping and e-cigarette usage, Sen. Rand Paul (R-Ky.) cautioned that any regulatory action, particularly a ban on all flavored e-cigarette products, would adversely affect adults, particularly those who are turning to e-cigarettes as a smoking cessation tool.

His solution, noting that it is already illegal for kids to be purchasing vaping and e-cigarette products, was to increase the penalties for those found selling to minors, adding that "most adults are using the flavors as well" and it could lead them back to combustible tobacco products if they are prevented from accessing flavored e-cigarettes.

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Cystic fibrosis symptoms improved // *continued from page 1*

fibrosis patients age 12 or older who had a single Phe508del allele. Patients in the combination group (n = 200) received 200 mg of elexacaftor once daily, 100 mg of tezacaftor once daily, and 150 mg of ivacaftor every 12 hours for 24 weeks. Patients in the other group (n = 203) received matched placebos.

At 14 weeks, patients in the combination group had a change in percentage of predicted forced expiratory volume in 1 second (FEV_1) that was 13.8 points higher than the placebo group (95% confidence interval, 12.1-15.4; *P* less than .001).

At 24 weeks, the combination group had a predicted FEV_1 difference that was 14.3 percentage points higher (95% confidence interval, 12.7-15.8, *P* less than .001). The rate of pulmonary exacerbations was 63% lower (rate ratio, 0.37; 95% CI, 0.25-0.55; *P* less than .001) and sweat chloride concentration was 41.8 mmol/L lower (95% CI, –44.4 to –39.3; *P* less than .001) in the combination group through 24 weeks.

At least one adverse event occurred in 93.1% of patients in the combination group and 96% of patients in the placebo group. Serious adverse events occurred in 28 patients (13.9%) in the combination group and 42 patients (20.9%) in the placebo group. There were no deaths in either group.

The study was funded by Vertex Pharmaceuticals. The authors had disclosures, including receiving personal fees and grants from various pharmaceutical companies and being on the advisory board, owning stock, or being an employee of Vertex Pharmaceuticals.

chestphysiciannews@chestnet.org

SOURCE: Middleton PG et al. 2019 Oct 31. N Engl J Med. doi: 10.1056/NEJMoa1908639.

VIEW ON THE NEWS

The dream of targeted therapies for cystic fibrosis may now be reality

After 30 years, new research from Middleton et al. and others appears to be the breakthrough we've been waiting for in treating cystic fibrosis, wrote Francis S. Collins, MD, PhD, of the National Institutes of Health in an accompanying editorial (N Engl J Med. 2019 Oct 31. doi: 10.1056/NEJMe1911602).

As one of the researchers who discovered the cystic fibrosis gene, he acknowledged the 3 decades of work that followed their discovery and the excitement that comes from being able to counter the common Phe508del CFTR mutation that afflicts so many cystic fibrosis patients. "These findings indicate that it may soon be possible to offer safe and effective molecularly targeted therapies to 90% of persons with cystic fibrosis," he wrote.

"Yet we must not abandon the patients with cystic fibrosis who have null mutations and will not have a response to these drugs," he added, noting that those challenges remain "substantial" and potentially will involve in vivo somatic-cell gene editing of airway epithelial cells. That said, what once was a dream 30 years ago now appears to be a reality.

Dr. Collins reported being a coinventor of the original patents on the CFTR gene, for which he donated all royalties to the Cystic Fibrosis Foundation.

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

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Vaping-injury patient received double-lung transplant

BY GREGORY TWACHTMAN
MDedge News

A Michigan teenager, described as an athlete and otherwise healthy, has survived a double-lung transplant following lung damage attributed to vaping.

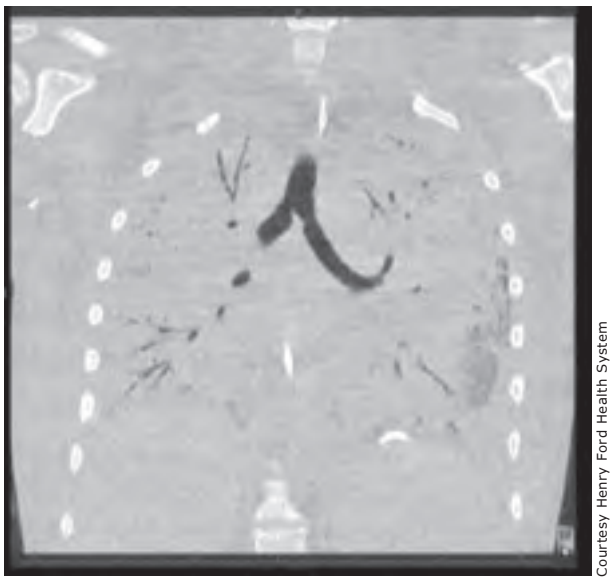
"On the 15th of October, the transplant team performed what we believe is the first double-lung transplant done in the nation for a vaping-injury victim, who is a teenager," Hassan Nemeh, MD, cardiothoracic surgeon with the Henry Ford Health System in Detroit, said during a Nov. 12, 2019, press conference to discuss the surgery.

"What I saw in his lungs is nothing that I have ever seen before, and I have been doing lung transplants for 20 years," Dr. Nemeh said. "There was an enormous amount of inflammation and scarring, in addition to multiple spots of dead tissue. The lung itself was so firm and scarred, we had to deliver it out of the chest. This is an evil that I haven't faced before."

He noted that the patient, now 17 years old but 16 when the surgical procedure occurred, is doing well in his recovery, and although the patient and the family are not yet ready to be identified, the health system made the decision to tell the story of the surgery as a cautionary tale.

"The reason we wanted to bring this case to public attention is because of the epidemic of e-cigarettes and vaping-induced lung injury that we are witnessing in the country," including more than 2,000 cases of injury and 39 deaths that have been confirmed from lung failure related to e-cigarettes and vaping that have been reported to the Centers for Disease Control and Prevention, he said.

"Our teenage patient would have faced certain death if it weren't for the lung transplant happening," Dr. Nemeh said, adding that, while vaping and e-cigarettes are being presented as a benign habit, there are potentially very deadly consequences that Henry Ford Hospital System wanted to highlight. He described the patient's lungs as essentially being nonfunctional with very little air being able to be passed into them, with the destruction to his native lung from pneumonia and dead tissue almost completely covering his lungs.



Courtesy Henry Ford Health System

A CT scan of the lungs of the patient with severe lung damage shows a very limited area of ventilation before his double-lung transplant.

This story began with a morning call on Oct. 1 from the Children's Hospital of Michigan alerting the Henry Ford Health System that they had a patient on life support because of complete lung failure who was not showing signs of healing and asking if the Henry Ford Health System could possibly handle a lung transplant for this patient.

Dr. Nemeh said that the patient was on a non-transportable extracorporeal membrane oxygenation (ECMO) machine at Children's. Dr. Nemeh and the team at Henry Ford determined that the situation for the patient was so dire that they put a portable ECMO machine into the trunk of Dr. Nemeh's car and delivered it to Children's in order to facilitate the transfer of the patient for transplantation surgery.

Victor Coba, MD, a critical care specialist and medical director of the ECMO program at Henry Ford, said: "We evaluated the irreversible lung damage that had occurred associated with vaping. Working closely with the lung transplant team and noting that his lungs would not recover, we worked to get him on the lung transplant list."

"We are here today to beg the public to pay special attention to the steps that were taken in this case," said Nicholas Yeldo, MD, anesthesiology and critical care specialist with Henry Ford. "Without the heroic measures that were taken in this case, this young patient would have died. There is no doubt about it."

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Vitamin E acetate and THC are common factors in vaping illness

// *continued from page 1*

tives of concern (such as plant oils, medium-chain triglyceride oil, petroleum distillates, and diluent terpenes) were not detected in BAL fluid specimens from EVALI patients.

BAL fluid specimens were collected from hospitalized EVALI patients in the course of their treatment, although not for the specific purpose of the CDC investigation, and sent to the CDC by public health laboratories and health departments in California, Connecticut, Hawaii, Illinois, Maryland, Michigan, Minnesota, Texas, Utah, and Wisconsin for analysis.

Dr. Schuchat stated that, as of Nov. 5, there have been 2,051 cases of EVALI reported to the CDC and 39 EVALI patients have died, with other deaths still under investigation as possibly related to EVALI. She said that the trend in new EVALI cases reported appears to be decreasing, but some states continue to see new cases. She cautioned that the lab findings of vitamin E acetate in BAL fluid do not rule out other possible compounds or ingredients that may contribute to EVALI and said the investigation will continue.

E-cigarette user survey

During the telebriefing, Jennifer Layden, MD, PhD, chief medical officer and state epidemiologist with the Illinois Department of Public Health (IDPH), gave an update on her department's efforts to investigate vaping behaviors that might have led to EVALI in e-cigarette users and also to obtain more information on sources of vaping devices that could be linked to EVALI. The data were also reported in a MMWR.

The IDPH conducted an online public survey during September 2019 and October 2019 targeting e-cigarette, or vaping, product users in Illinois. The survey was promoted via social media on the IDPH website, local health departments, and other outlets. The survey yielded 4,631 respondents who answered questions about the frequency of vaping, sources of supply, and types of substances used. The investigators were then able to compare vaping-use habits and behaviors with similar information gleaned from EVALI patients.

Among survey respondents, 94% reported using any nicotine-containing e-cigarette, or vaping, products in the past 3 months; 21% used any THC-containing products; and 11% used both THC-containing products and nicotine-containing products. THC-containing product use was highest among survey respondents aged 18-24 years (36%) and decreased with increasing age. Compared with these survey respondents, EVALI patients were more likely to report exclusive use of THC-containing products (adjusted odds ratio, 2.0; 95% confidence interval, 1.1-3.6), frequent use (more than five times per day) of these products (aOR, 3.1; 95% CI, 1.6-6.0), and obtaining these products from informal sources, such as from a dealer, off the street, or from a friend (aOR, 9.2; 95% CI, 2.2-39.4). In addition, "the odds of using Dank Vapes, a class of largely counterfeit THC-containing products, was also higher among EVALI patients" (aOR, 8.5; 95% CI, 3.8-19.0), according to the MMWR.

Recommendations

CDC recommends that people should not buy any type of e-cigarette, or vaping, products, particularly those containing THC, off the street. They should also refrain from modifying or adding any substances to e-cigarette, or vaping, products that are not intended by the manufacturer, including products purchased through retail establishments.

Dr. Layden concluded, "we are in a better place today than we were a few weeks ago in terms of having one very strong culprit of concern based on the lung fluid testing," but since the specific substances causing lung injury are not yet known, the only way to ensure that individuals are not at risk while the investigation continues is to consider refraining from use of all vaping products.

For more information and resources, visit For the Public, For Healthcare Providers, and For Health Departments pages, as well as the CDC's Publications and Resources page.

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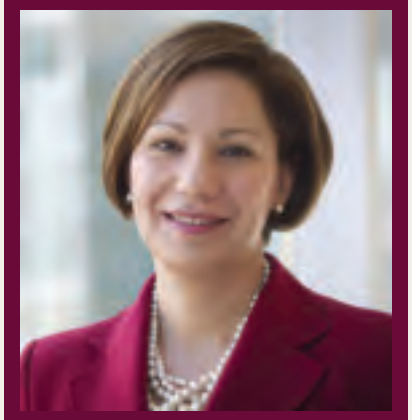

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INNOVATIVE MEDICINE **Best Practices**

Treatment of Unresectable Stage III Non-small Cell Lung Cancer

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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Previously healthy patients hospitalized for sepsis show increased mortality risk

BY MITCHEL L. ZOLER
MDedge News

WASHINGTON – Although severe, community-acquired sepsis in previously healthy U.S. adults is relatively uncommon, it occurs often enough to strike about 40,000 people annually, and when previously healthy people are hospitalized for severe sepsis, their rate of in-hospital mortality was double the rate in people with one or more comorbidities who have severe, community-acquired sepsis, based on a review of almost 7 million Americans hospitalized for sepsis.

The findings "underscore the importance of improving public awareness of sepsis and emphasizing early sepsis recognition and treatment in all patients," including those without comorbidities, Chanu Rhee, MD, said at an annual scientific meeting on infectious diseases. He hypothesized that the increased sepsis mortality among previously healthy patients may have stemmed from factors such as delayed sepsis recognition resulting in hospitalization at a more advanced stage and less aggressive management.

In addition, "the findings provide context for high-profile reports about sepsis death in previously healthy people," said Dr. Rhee, an infectious diseases and critical care physician at Brigham and Women's Hospital in Boston. Dr. Rhee and associates found that, among patients hospitalized with what the researchers defined as "community-acquired" sepsis, 3% were judged previously healthy by having no identified major or minor comorbidity or pregnancy at the time of hospitalization, a percentage that – while small – still translates into roughly 40,000 such cases annually in the United States.

The study used data collected on hospitalized U.S. patients in the Cerner Health Facts, HCA Healthcare, and Institute for Health Metrics and Evaluation databases, which included about 6.7 million people total including 337,983 identified as having community-acquired sepsis, defined as patients who met the criteria for adult sepsis advanced by the Centers for Disease Control and Prevention within 2 days of their hospital admission. The researchers looked further into the hospital records of these patients and divided them into patients with one or more major comorbidities (96% of the cohort); patients who were pregnant or had a "minor" comorbidity such as a lipid disorder, benign neoplasm, or obesity (1% of the study group); or those with no chronic comorbidity (3%; the subgroup the researchers deemed previously healthy).


Mitchel L. Zoler/MDedge News

Dr. Chanu Rhee

In a multivariate analysis that adjusted for patients' age, sex, race, infection site, and illness severity at the time of hospital admission the researchers found that the rate of in-hospital death among the previously healthy patients was exactly twice the rate of those who had at least one major chronic comorbidity, Dr. Rhee reported. Differences in the treatment received by the previously healthy patients or in their medical status compared with patients with a major comorbidity suggested that the previously health patients were sicker. They had a higher rate of mechanical ventilation, 30%, compared with about 18% for those with a comorbidity; a higher rate of acute kidney injury, about 43% in those previously healthy and 28% in those with a comorbidity; and a higher percentage had an elevated lactate level, about 41% among the previously healthy patients and about 22% among those with a comorbidity.

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SOURCE: Alrawashdeh M et al. Open Forum Infect Dis. 2019 Oct 23;6. Abstract 891.

Rivaroxaban approved for VTE prevention in acutely ill

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has approved rivaroxaban (Xarelto) for the prevention of venous thromboembolism (VTE) in hospitalized, acutely ill patients at risk for thromboembolic complications who do not have a high bleeding risk, according to a release from Janssen.

FDA approval for the new indication is based on results from the phase 3 MAGELLAN and MARINER trials, which included more than 20,000 hospitalized, acutely ill patients. In MAGELLAN, rivaroxaban demonstrated noninferiority to enoxaparin, a low-molecular-weight heparin, in short-term usage, and it was superior over the long term, compared with short-term enoxaparin followed by placebo.

While VTE and VTE-related deaths were not reduced in MARINER, compared with placebo, patients who received rivaroxaban did see a significantly reduction in symptomatic VTE with a favorable safety profile.

According to the indication, rivaroxaban can be administered to patients during hospitalization and can be continued after discharge for 31-39 days. The safety profile in MAGELLAN and MARINER was consistent with that already seen, with the most common adverse event being bleeding.

"With this new approval, Xarelto as an oral-only option now has the potential to change how acutely ill medical patients are managed for the prevention of blood clots, both in the hospital and for an extended period after discharge," said Alex C. Spyropoulos, MD, of Northwell Health at Lenox Hill Hospital, New York, and a member of the steering committee of the MAGELLAN trial.

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Starting PCSK9 in acute-phase ACS under study

BY BRUCE JANCIN
MDedge News

PARIS – The first-ever randomized trial of in-hospital initiation of a PCSK9 inhibitor on top of guideline-recommended high-intensity statin therapy in the very-high-risk acute phase of an acute coronary syndrome (ACS) safely resulted in dramatically lower LDL cholesterol levels than with early prescribing of a high-intensity statin alone, Konstantinos C. Koskinas, MD, reported at the annual congress of the European Society of Cardiology.

At 8 weeks of follow-up, 90% of the dual-therapy group had achieved the new ESC guideline-recommended target of an LDL cholesterol less than 55 mg/dL, compared with 11% of patients randomized to high-intensity atorvastatin at 40 mg/day plus placebo injections. Moreover, 96% of patients on atorvastatin 40 mg/day plus evolocumab at 420 mg per subcutaneous injection were below the former target of an LDL cholesterol less than 70 mg/dL, as were 38% of those on the high-intensity statin alone, according to Dr. Koskinas, a cardiologist at the University of Bern (Switzerland).

The seven-center Swiss EVOPACS trial, featuring 308 ACS patients, could be considered a proof-of-concept study, as it lacked the size and duration to be powered to assess clinical outcomes.

"The clinical impact of very early LDL lowering with evolocumab initiated in the acute setting of ACS warrants further investigation in a dedicated cardiovascular outcomes trial," Dr. Koskinas asserted. "We see this as the natural next step. Discussions are underway about a long-term trial with clinical endpoints, but no decisions have been made."

The rationale for the EVOPACS trial is based upon current standard practice in ACS management, which includes initiation of a high-intensity statin during the acute phase of ACS, a particularly high-risk period for recurrent events. This practice has a Class IA recommendation in the guidelines based on published evidence that it results in a significantly reduced rate of the composite of death, MI, or rehospitalization for ACS within 30 days, compared with a less aggressive approach to LDL cholesterol lowering.

Yet even though the PCSK9 inhibitors are the 800-lb gorillas of LDL cholesterol lowering, they've never been tested in the setting of acute-phase ACS. For example, in the landmark ODYSSEY OUTCOMES trial, alirocumab was initiated on average 2.6 months after ACS, while in FOURIER the lag time between ACS and the start of evolocumab was 3.4 years, the cardiologist noted.

In contrast, all of the 37% of EVOPACS participants with an ST-segment elevation MI were enrolled in the study and on treatment within 24 hours after symptom onset. So were more than one-third of those with non–ST-elevation ACS, with the remainder getting onboard 24-72 hours after symptom onset.

The safety and tolerability of dual LDL cholesterol–lowering therapy were excellent in the brief EVOPACS study. There were no significant between-group differences in adverse events or serious adverse events, nor in prespecified events of special interest, including muscle pain, neurocognitive changes, or elevated liver enzyme levels.

The LDL cholesterol lowering achieved with dual therapy in EVOPACS was jaw dropping: Over the course of 8 weeks, the mean LDL cholesterol went from 132 to 31 mg/dL. In patients on early high-intensity atorvastatin alone, LDL cholesterol went from 139 to 80 mg/dL.

The full details of the EVOPACS trial have been published (J Am Coll Cardiol. 2019 Aug 16. doi: 10.1016/j.jacc.2019.08.010).

The trial was funded by Amgen. Dr. Koskinas reported receiving honoraria from Amgen and Sanofi.

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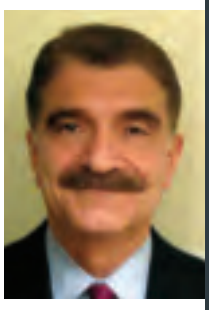
VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: PCSK9 inhibitors are monoclonal antibodies that inhibit proprotein convertase subtilisinkexin 9 in the liver leading to a profound lowering of the LDL cholesterol in the blood. But unlike statins, these drugs are used by injection. By targeting the patients with ACS and starting the drug early after the event, this trial showed dramatic lowering of the LDL cholesterol. Whether the clinical outcomes will follow the lower LDL level was not addressed by this trial and we will have to wait the results of larger trials focused on patients' clinical outcomes.

Insomnia symptoms increase likelihood of stroke

BY JAKE REMALY
MDedge News

The presence of insomnia symptoms increases the likelihood of cardiovascular or cerebrovascular disease during approximately 10 years of follow-up, according to a large cohort study of adults in China. A greater number of insomnia symptoms is associated with increased risk, and this relationship is more evident in younger adults and in adults without hypertension at baseline, researchers reported Nov. 6 in Neurology.

"These results suggest that, if we can target people who are having trouble sleeping with behavioral therapies, it's possible that we could reduce the number of cases of stroke, heart attack, and other diseases later down the line," study author Liming Li, MD, professor of epidemiology at Peking University, Beijing, said in a news release.

To clarify the relationships between individual insomnia symptoms, cardiocerebral vascular diseases, and potential effect modifiers, Dr. Li and colleagues analyzed data from the China Kadoorie Biobank Study. For this study, more than 500,000 adults in China aged 30-79 years completed a baseline survey during 2004-2008. The present analysis included data from 487,200 participants who did not have a history of stroke, coronary heart disease, or cancer at baseline.

For the baseline survey, participants answered questions about whether specific insomnia symptoms occurred at least 3 days per week during the past month. The symptoms included difficulty initiating or maintaining sleep (that is, sleep-onset latency of 30 minutes or more after going to bed or waking up in the middle of the night); waking too early and being unable to fall back asleep; and trouble functioning during the day because of bad sleep.

The researchers assessed the incidence of cardiocerebral vascular diseases through 2016 by examining disease registries, national health insurance claims databases, and local records. Investigators identified participants with any cardiocerebral vascular disease and assessed the incidence of ischemic heart disease, acute myocardial infarction, hemorrhagic stroke, and ischemic stroke. The researchers followed each participant until the diagnosis of a cardiocerebral vascular disease outcome, death from any cause, loss to follow-up, or Dec. 31, 2016. The researchers used Cox proportional hazard models to estimate hazard ratios for the association between each insomnia symptom and cardiocerebral vascular disease outcomes. They adjusted the models for established and potential confounding factors, including age, income, smoking status, diet, and physical activity.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The results of this large observational study are interesting, especially for those of us treating patients with sleep disorders. Patients baseline characteristics such as older age, female gender, and low socioeconomic and education profile are known risk factors for higher cardiovascular events. The study, however, did not look at the impact of these patients' baseline profiles on the higher incidence of cardiocerebral vascular events.

More than 16% had any insomnia symptom

Of the 487,200 participants, 11.3% had difficulty initiating or maintaining sleep, 10.4% had early-morning awakening, and 2.2% had

Continued on following page

Continued from previous page

daytime dysfunction attributed to poor sleep. Compared with participants without insomnia symptoms, participants with insomnia symptoms tended to be older and were more likely to be female, not married, and from a rural area. In addition, those with insomnia symptoms were more likely have depression or anxiety symptoms, lower education level, lower household income, and lower body mass index. They also were more likely to have a history of diabetes mellitus. During a median follow-up of 9.6 years, 130,032 cases of cardiocerebral vascular disease occurred, including 40,348 cases of ischemic heart disease and 45,316 cases of stroke.

After adjustment for potential confounders, each insomnia symptom was associated with greater risk of cardiocerebral vascular disease. For difficulty initiating or maintaining sleep, the hazard ratio was 1.09. For early-morning awakening, the HR was 1.07. For daytime dysfunction, the HR was 1.13. Each insomnia symptom was associated with increased risk of ischemic heart disease and ischemic stroke, whereas only difficulty initiating or maintaining sleep was associated with increased risk of acute MI.

In all, 16.4% of participants reported any insomnia symptom; 10% had one symptom, 5.2% had two symptoms, and 1.2% had three symptoms. "Compared with those without any insomnia symptoms, participants with one, two, or three symptoms had a 7%, 10%, or 18% higher risk of total [cardiocerebral vascular disease] incidence, respectively," the authors wrote. "Our study is the first large-scale cohort study that identified positive dose-response relationships between the number of insomnia symptoms and risks of [cardiocerebral vascular diseases, ischemic heart disease] and stroke incidence."

Opportunity for intervention

Compared with clinical diagnostic criteria for insomnia, "individual insomnia symptoms are better defined and more feasible to assess with questionnaires in large-scale population studies and clinical practice," Dr. Li and colleagues wrote. "Moreover, it is reasonable that insomnia symptoms are more modifiable and precisely targetable through behavioral therapies before developing into clinically significant insomnia disorder. Therefore, future clinical trials or community-based intervention studies should be conducted to test whether lifestyle or sleep hygiene interventions for insomnia symptoms can reduce subsequent [cardiocerebral vascular disease] risks."

The results suggest that efforts aimed at early detection and intervention should include a focus on younger adults and people who do not have high blood pressure, Dr. Li said.

This study was supported by the National Key Research and Development Program of China, the Chinese Ministry of Science and Technology, and the National Natural Science Foundation of China. The China Kadoorie Biobank surveys were supported by grants from the Kadoorie Charitable Foundation and the U.K. Wellcome Trust. The authors had no relevant disclosures.

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Dupilumab effective in early- and late-onset asthma

BY JENNIFER SMITH
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – A new analysis suggests dupilumab is beneficial for patients with early- or late-onset asthma.

Dupilumab may be more effective in reducing severe asthma exacerbations in patients with late-onset asthma, but the drug's effect on lung function appeared the same regardless of asthma onset. Nicola Hanania, MD, of Baylor College of Medicine in Houston presented these results at the annual meeting of the American College of Chest Physicians.

Dr. Hanania and colleagues conducted a subanalysis of the LIBERTY ASTHMA QUEST study (NCT02414854). Previous data from this study showed that patients with uncontrolled, moderate to severe asthma who received dupilumab had fewer exacerbations and better lung function than did patients who received placebo (N Engl J Med. 2018;378:2486-96).

In their subanalysis, Dr. Hanania and his colleagues evaluated the efficacy of dupilumab, given at 200 mg or 300 mg every 2 weeks, in patients with early-onset asthma (at 40 years of age or younger) and late-onset asthma (at 41 years or older). The analysis included 919 patients with early-onset asthma who received dupilumab and 450 early-onset patients who received placebo. There were 345 patients with late-onset asthma who received dupilumab and 188 late-onset patients who received placebo.

Jennifer Smith/MDedge News

Dr. Nicola Hanania

Exacerbations

Dupilumab significantly reduced the adjusted annualized severe exacerbation rates during the 52-week treatment period. Significant reductions occurred in both early- and late-onset patients, though reductions were greater in the late-onset group.

In early-onset patients, dupilumab reduced severe exacerbations by 38% when given at 200 mg and by 37% when given at 300 mg (*P* less than .001 vs. placebo). In late-onset patients, dupilumab reduced exacerbations by 64% and 69%, respectively (*P* less than .001 vs. placebo).

Dr. Hanania went on to note that reductions in exacerbation rates were greatest in patients with elevated blood eosinophils (150 cells/mcL or greater) or fractional exhaled nitric oxide (FeNO; 25 ppb or greater).

In patients with early-onset asthma and elevated eosinophils, dupilumab reduced severe exacerbations by 50% when given at 200 mg and by 55% when given at 300 mg (*P* less than .001 vs. placebo). In late-onset patients with elevated eosinophils, dupilumab reduced exacerbations by 65% and 73%, respectively (*P* less than .001 vs. placebo).

In patients with early-onset asthma and elevated FeNO, dupilumab reduced severe exacerbations by 56% when given at 200 mg and by 52% when given at 300 mg (*P* less than .001 vs. placebo). In late-onset patients with elevated FeNO, dupilumab reduced exacerbations by 79% and 71%, respectively (*P* less than .001 vs. placebo).

Lung function

Dupilumab also improved pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV_1), compared with placebo, with similar results in early- and late-onset patients.

In early-onset patients, the *P* values were less than .001 for both doses of dupilumab at weeks 12 and 52. In late-onset patients, the *P* values were less than .001 for the 300-mg dose at week 12 and the 200-mg dose at week 52, less than .01 for the 200-mg dose at week 12, and less than .05 for the 300-mg dose at week 52.

The effects of dupilumab on pre-BD FEV_1 were greatest in patients with elevated eosinophils or FeNO. At week 12, the *P* value was less than .001 for both doses of dupilumab in early-onset patients with elevated eosinophils or FeNO.

This research was sponsored by Sanofi and Regeneron. Dr. Hanania disclosed relationships with Genentech, Novartis, AstraZeneca, Boehringer Ingelheim, GSK, Regeneron, and Sanofi.

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SOURCE: Hanania N et al. CHEST 2019; Abstract. doi: 10.1016/j.chest.2019.08.870.

Omalizumab results for asthma varied with fixed airflow obstruction, reversibility

BY JENNIFER SMITH
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – A new analysis suggests omalizumab reduces exacerbations in patients with severe, uncontrolled asthma, regardless of fixed airflow obstruction (FAO). However, exacerbation reductions were greatest in patients with high reversibility, and omalizumab only improved lung function significantly in FAO-negative patients with high reversibility.

Nicola Hanania, MD, of Baylor College of Medicine, Houston, presented these findings at the annual meeting of the American College of Chest Physicians.

The findings are from a post hoc analysis of the phase 3 EXTRA study (NCT00314574). This 48-week study enrolled patients who had inadequately controlled, severe asthma despite receiving high-dose inhaled corticosteroids and long-acting beta-agonists.

The patients were randomized to receive omalizumab (n = 427) or placebo (n = 421). Baseline characteristics were similar between the treatment arms.

FAO presence was defined as a postbronchodilator FEV_1/FVC (forced expiratory volume in 1 second/forced vital capacity) ratio less than 70%. High reversibility was defined as an increase in FEV1 of 12% or greater after albuterol administration.

Omalizumab reduced exacerbations regardless of FAO, but the exacerbation relative rate reductions were greatest in FAO-positive and -negative subgroups with high reversibility.

The exacerbation relative rate reductions with omalizumab versus placebo were as follows:

- 24.8% in the overall population.
- 6.0% in FAO-positive patients with low reversibility.
- 59.8% in FAO-positive patients with high reversibility.
- 17.4% in FAO-negative patients with low reversibility.
- 44.3% in FAO-negative patients with high reversibility.

"So bronchodilator reversibility at baseline was … a correlate of more significant exacerbation reduction than … low reversibility," Dr. Hanania said. "But the fixed airflow obstruction, whether it was present or not, did not really matter."

As for lung function improvement, omalizumab conferred a marginal benefit for the overall population, but the improvement was "much more significant" in the FAO-negative patients with high reversibility, according to Dr. Hanania.

At week 48, the least-square mean treatment difference (omalizumab vs. placebo) for absolute FEV_1 change from baseline was:

- 68 mL in the overall population.
- 17 mL in FAO-positive patients with low reversibility.
- 2 mL in FAO-positive patients with high reversibility.
- 34 mL in FAO-negative patients with low reversibility.
- 104 mL in FAO-negative patients with high reversibility.

"As lung function improvement by omalizumab appeared to be driven by reversibility, asthma with lower reversibility and fixed airflow obstruction may represent a different phenotype," Dr. Hanania said. "I think this needs to be looked at."

This research was funded by Genentech and Novartis. Dr. Hanania disclosed relationships with Genentech, Novartis, AstraZeneca, Boehringer Ingelheim, GSK, Regeneron, and Sanofi.

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SOURCE: Hanania N et al. CHEST 2019; Abstract. doi: 10.1016/j.chest.2019.08.869.

Physicians, patients may overestimate asthma control

BY JENNIFER SMITH
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – Physicians and patients both overestimate control of severe asthma, according to an observational study.

More than half (53%) of cases physicians rated as controlled were actually uncontrolled according to the Asthma Control Test (ACT), and 30% of patients who considered their asthma controlled actually had uncontrolled asthma according to the ACT.

Reynold A. Panettieri Jr., MD, of Rutgers University in New Brunswick, N.J., presented these findings at the annual meeting of the American College of Chest Physicians.

The findings are from CHRONICLE study, an ongoing observational study of adults with severe asthma who are being treated by U.S. allergists or pulmonologists. The study enrolled 796 patients during Feb. 2018–Feb. 2019, and 482 of them were evaluable because they completed the necessary surveys.

Patients received care from an allergist (49%), a pulmonologist (38%), or both (13%). Patients were treated with biologics (n = 370), maintenance systemic corticosteroids (n = 64), or high-dosage inhaled corticosteroids with additional controllers (n = 90).

At patient enrollment, physicians reported their assessment of patients' asthma control and completed the 5-point Global Evaluation of Treatment Effectiveness (GETE). The physicians' assessments of patients were informed by the patients' verbal reports (50%), lung function testing (44%), in-office ACT (41%), and recent exacerbations (39%).

Patients also completed the ACT and GETE online at the time of enrollment. Neither patients nor physicians were privy to the other group's responses.

Overall, physicians said 279 patients had controlled asthma. However, according to the ACT, 27% of these cases were very poorly controlled, 26% were not well controlled, and 47% were well controlled.

"So [when] we as a provider say the patient's controlled, we're wrong half the time," Dr. Panettieri said.

However, physicians were more accurate when deeming patients' asthma uncontrolled. Physicians said 201 cases of asthma were uncontrolled, and the ACT said 64% of these cases were very poorly controlled, 22% were not well controlled, and 13% were well controlled.

Compared with the physicians' results, the patients' reports were more in line with ACT results. However, the patients still overestimated control.

"About 99% of the time, when a patient tells you they're uncontrolled, they're uncontrolled by the ACT," Dr. Panettieri said.

This study is supported by AstraZeneca. Dr. Panettieri disclosed relationships with AstraZeneca, Sanofi, Regeneron, Genentech, and Novartis.

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SOURCE: Panettieri RA et al. CHEST 2019; Abstract. doi. 10.1016/j.chest.2019.08.272.

Digital inhaler reveals uncontrolled asthma

BY JENNIFER SMITH
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – Data collected by the ProAir Digihaler suggest patients with previous, but not current, severe clinical asthma exacerbations may still use their rescue inhalers daily and therefore require additional therapy.

Researchers studied asthma patients who had experienced exacerbations in the previous year. Patients who also had exacerbations while on study used the ProAir Digihaler about twice a day, on average. Patients without on-study exacerbations used the ProAir Digihaler an average of 1.14 times per day.

The daily use among patients without exacerbations suggests their asthma is "still quite uncontrolled," and, according to guidelines, they may

require additional therapy, said Roy Pleasants, PharmD, of the University of North Carolina at Chapel Hill.

Dr. Pleasants presented these findings at the annual meeting of the American College of Chest Physicians.

He and his colleagues conducted a phase 3 study (NCT02969408) of ProAir Digihaler use in adults who had at least one severe clinical asthma exacerbation in the previous 12 months. They had an Asthma Control Questionnaire score of 1.5 or greater, were on moderate-dose inhaled corticosteroids (with or without a long-acting beta-agonist), and had stable asthma controller dosing for at least 3 months.

For this study, the ProAir Digihaler replaced patients' other rescue medications. The ProAir Digihaler is a digital inhaler that delivers 90 mcg of albuterol per dose, detects the date and time a dose was prepared, and records the inhalation profile. Over a 12-week period, the ProAir Digihaler recorded each use, which was defined as consecutive inhalations within 60 seconds.

Of the 381 patients enrolled in the study, 360 (94.5%) made at least one valid inhalation. The mean age of these patients was 50 years, and 80.6% were female. Of the 360 patients, 64 experienced 78 exacerbations while on study.

Most episodes of inhaler use consisted of a single inhalation (58.9%), although 35.8% consisted of two inhalations, 3.5% consisted of three inhalations, and 1.8% consisted of four or more inhalations.

Jennifer Smith/MDedge News

Dr. Roy Pleasants

The mean peak inspiratory flow was 73.18 L/min (standard deviation [SD], 20.33) in patients without exacerbations. Among patients with exacerbations, the mean peak inspiratory flow was 71.36 (SD, 23.80) during exacerbation and 74.71 L/min (SD, 22.46) outside the exacerbation window, which was 14 days before and after the exacerbation peak.

The mean inhalation volume was 1.45 L (SD, 0.75) among patients without exacerbations, 1.44 L (SD, 0.66) outside the exacerbation window, and 1.44 L (SD, 0.76) during exacerbation. The mean inhalation duration was 1.62 sec (SD, 0.88), 1.59 sec (SD, 0.77), and 1.61 sec (SD, 0.82), respectively.

"If you look at the inhalation volume in the 64 patients who exacerbated, it really didn't change during exacerbation," Dr. Pleasants noted. "Essentially, you can say the same thing about inhalation duration."

This study was sponsored by Teva, makers of the ProAir Digihaler. Dr. Pleasants disclosed relationships with Teva, Grifols, Sunovion, and Boehringer Ingelheim.

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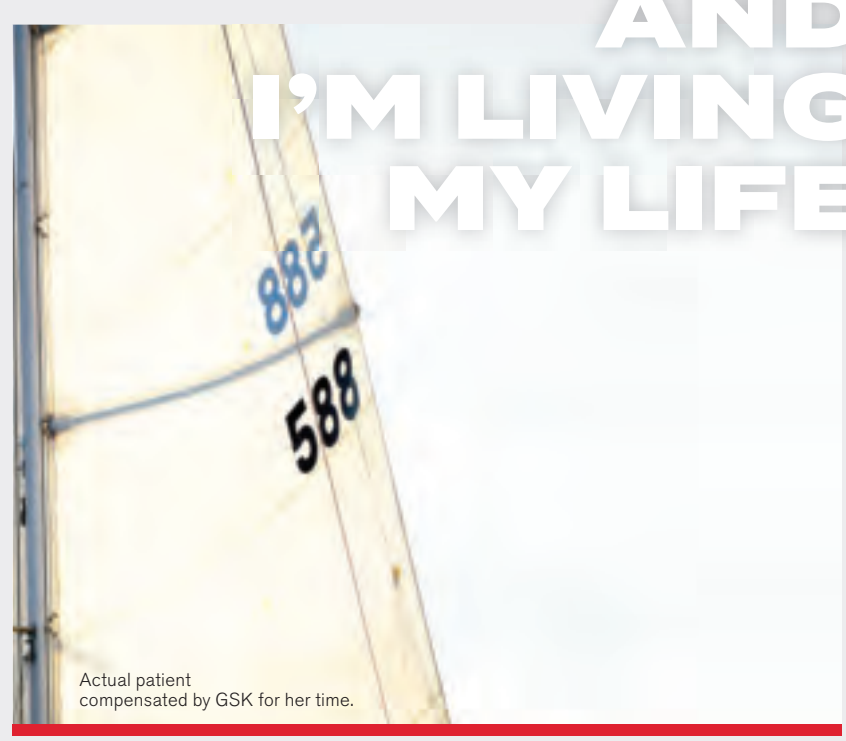
SOURCE: Pleasants R et al. CHEST 2019; Abstract. doi: 10.1016/j.chest.2019.08.273.

NUCALA is indicated for the add-on maintenance treatment of patients 6 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.



#1 prescribed biologic indicated for severe eosinophilic asthma*— 38,000 patients and counting[1†]

*Source: IQVIA - NPA™ audit: 12 mo. TRX data ending 4/19 (All rights reserved).

†December 2015 to April 2019 data sourced from IQVIA and GSK. Claims data based on total number of unique patients who had at least one claim for NUCALA in the United States. Not all patients remained on therapy. Individual results may vary.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred with NUCALA compared to none with placebo. Consider vaccination if medically appropriate.

Reduction of Corticosteroid Dosage

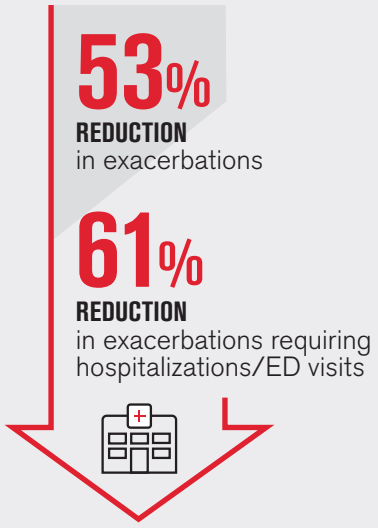
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms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

Parasitic (Helminth) Infection

Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until infection resolves.

Choose NUCALA:

Powerful Protection From Exacerbations[2‡]



Powerful Reduction in OCS Dose[3]

Lasting Evidence[4]

Only anti-interleukin 5 (IL-5) with a

4.5-year

open-label study that evaluated safety and efficacy

MENSA (Trial 2)[2]: 32-week study comparing NUCALA 100 mg to placebo, each added to SOC in 576 patients aged ≥12 years with severe eosinophilic asthma (SEA). **Primary Endpoint Results:** Frequency of exacerbations. NUCALA: 0.83/year, placebo: 1.74/year; *P*<0.001). **Secondary Endpoint Results:** Frequency of exacerbations requiring hospitalization and/or ED visit; NUCALA: 0.08/year; placebo: 0.20/year; *P*=0.02.

SIRIUS (Trial 3)[3]: 24-week study comparing NUCALA 100 mg to placebo in 135 patients aged ≥12 years with SEA receiving prednisone 5-35 mg (or equivalent) per day and regular use of high-dose ICS and 1 other controller. **Primary Endpoint Results:** Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control vs placebo; *P*=0.008.

COLUMBA[4]: 4.5-year open-label study assessing the safety, immunogenicity, and efficacy of NUCALA 100 mg added to asthma controller therapy in 347 patients aged ≥12 years with SEA.

‡ Worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalizations and/or emergency department (ED) visits; for patients on maintenance oral/systemic corticosteriods, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

Standard of care (SOC)=regular treatment with high-dose inhaled corticosteroids (ICS) and at least 1 other controller with or without oral corticosteroids (OCS).

Learn more at **KnowNucalaHCP.com**

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasms, 3% (<1%).

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for NUCALA and 5% for placebo. Manifestations included rash, flushing, pruritus, headache, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection site reactions (eg, pain, erythema, swelling, itching, burning sensation) occurred in subjects treated with NUCALA.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothertobaby.org/asthma.

The data on pregnancy exposures are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters.

References: 1. Data on file, GSK. **2.** Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371:1198-1207. **3.** Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371:1189-1197. **4.** Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol.* 2019;143(5):1742-1751.

Please see Brief Summary of Prescribing Information for NUCALA on the following pages.

MPLJRNA190008 September 2019
Produced in USA.

Nucala
(mepolizumab)
Injection 100 mg/mL

BRIEF SUMMARY

NUCALA
(mepolizumab) for injection, for subcutaneous use
The following is a brief summary only and is focused on the indication for maintenance treatment of severe asthma with an eosinophilic phenotype. See full prescribing information for complete product information.

1 INDICATIONS AND USAGE
1.1 Maintenance Treatment of Severe Asthma
NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype.
Limitation of Use: NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS
NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

5.3 Opportunistic Infections: Herpes Zoster
Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials *[see Adverse Reactions (6.1)]*. Consider vaccination if medically appropriate.

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

5.5 Parasitic (Helminth) Infection
Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

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.

6.1 Clinical Trials Experience in Severe Asthma
Adult and Adolescent Subjects Aged 12 Years and Older
A total of 1,327 subjects with severe asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trial 1, NCT #01000506; Trial 2, NCT #01691521; and Trial 3, NCT #01691508). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1) of full prescribing information]*. Of the subjects enrolled, 59% were female, 85% were white, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.
The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Subjects with Severe Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial: Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects receiving mepolizumab 75 mg IV compared with 2 subjects in the placebo group.
Systemic Reactions, including Hypersensitivity Reactions: In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA 100 mg. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA 100 mg. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA 100 mg and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.
Injection Site Reactions: Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects receiving NUCALA 100 mg compared with 3% in subjects receiving placebo.
Long-term Safety: Nine hundred ninety-eight subjects received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.
Pediatric Subjects Aged 6 to 11 Years
The safety data for NUCALA is based upon 1 open-label clinical trial that enrolled 36 subjects with severe asthma aged 6 to 11 years. Subjects received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of NUCALA administered subcutaneously once every 4 weeks. Subjects received NUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 subjects received NUCALA for a further 52 weeks (long phase). The adverse reaction profile for subjects aged 6 to 11 years was similar to that observed in subjects aged 12 years and older.

6.3 Immunogenicity
In adult and adolescent subjects with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 subject with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 or 100 mg, 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.
The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.4 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. 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 NUCALA or a combination of these factors.
Immune System Disorders: Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS
Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.
Risk Summary: The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and 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 mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 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 Embryofetal 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 mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an area under the curve [AUC] basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys.
Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.
In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation
Risk Summary
There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use
The safety and efficacy of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older.
Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT #01691521) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1) of full prescribing information.]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received 100 mg and the mean apparent clearance in these subjects was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.

(continued on next page)

8 USE IN SPECIFIC POPULATIONS *(cont'd)*
Use of NUCALA in children aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single, open-label clinical trial (NCT #02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg SC every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg SC *[see Clinical Pharmacology (12.3) of full prescribing information]*.
The efficacy of NUCALA in children aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents *[see Clinical Pharmacology (12.3) of full prescribing information]*. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2) of full prescribing information]*.
The safety and efficacy in pediatric patients aged younger than 6 years with severe asthma have not been established.

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 46) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE
Single doses of up to 1,500 mg have been administered intravenously to adult subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.
There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.
Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week.

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.
Advise the patient to read the FDA-approved patient labeling (Patient Information).
Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.
Not for Acute Symptoms or Deteriorating Disease
Inform patients that NUCALA 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 NUCALA.
Opportunistic Infections: Herpes Zoster
Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.
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.
Pregnancy Exposure Registry
Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations (8.1)]*.

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Tide beginning to turn on vaccine hesitancy

BY DOUG BRUNK
MDedge News

NEW ORLEANS – In the opinion of Paul A. Offit, MD, pushback against antivaccination campaigns and advocates is stronger than ever.

The shift began with the measles outbreak in Southern California in late 2014, he said. According to the Centers for Disease Control and Prevention, 125 measles cases with rash that occurred between Dec. 28, 2014, and Feb. 8, 2015, were confirmed in U.S. residents. Of these, 100 were California residents (MMWR. 2015 Feb 20;64[06];153-4).

"This outbreak spread ultimately to 25 states and involved 189 people," Dr. Offit said at the annual meeting of the American Academy of Pediatrics. "It was in the news almost every day. As a consequence, there were measles outbreaks in New York, New Jersey, Florida, Oregon, and Texas, and Washington, which began to turn the public sentiment against the antivaccine movement."

Even longstanding skeptics are changing their tune. Dr. Offit, professor of pediatrics in the division of infectious diseases at the Children's Hospital of Philadelphia, cited a recent study from the Autism Science Foundation which found that 85% of parents of children with autism spectrum disorder don't believe that vaccines cause the condition. "Although there will be parents who continue to believe that vaccines cause autism, most parents of children with autism don't believe that," he said. "Also, it's a little hard to make your case that vaccines are dangerous and that you shouldn't get them in the midst of outbreaks."

Perhaps the greatest pushback against antivaccination efforts has been made in the legal arena. In 2019 alone, legislators in California banned parents from not vaccinating their kids because of personal beliefs, while lawmakers in New York repealed the religious exemption to vaccinate, those in Maine repealed the religious and philosophical exemption, those in New Jersey required detailed written explanation for religious exemption, and those in Washington State repealed the philosophical exemption for the MMR vaccine.

Pushback also is apparent on various social media platforms. For example, Dr. Offit said, Pinterest restricts vaccine search results to curb the spread of misinformation, YouTube removes ads from antivaccine channels, Amazon Prime has pulled antivaccination documentaries from its video service, and Facebook has taken steps to curb misinformation about vaccines. "With outbreaks and with children suffering, the media and public sentiment has largely turned against those who are vehemently against vaccines," he said. "I'm talking about an angry, politically connected, lawyer-backed group of people who are conspiracy theorists, [those] who no matter what you say, they're going to believe there's a conspiracy theory to hurt their children and not believe you. When that group becomes big enough and you start to see outbreaks like we've seen, then it becomes an issue. That's where it comes down to legislation. Is it your inalienable right as a U.S. citizen to allow your child to catch and transmit a potentially fatal infection? That's what we're struggling with now."


Doug Brunk/MDedge News
Dr. Paul A. Offit

When meeting with parents who are skeptical about vaccines or refuse their children to have them, Dr. Offit advises clinicians to "go down swinging" in favor of vaccination. He shared how his wife, Bonnie, a pediatrician who practices in suburban Philadelphia, counsels parents who raise such concerns. "The way she handled it initially was to do the best she could to eventually get people vaccinated," he said. "She was successful about one-quarter of the time. Then she drew a line. She started saying to parents, 'Look; don't put me in a position where you are asking me to practice substandard care. I can't send them out of this room knowing that there's more measles out there, knowing that there's mumps out there, knowing that there's whooping cough out there, knowing that there's pneumococcus and varicella out there. If this child leaves this office and is hurt by any of those viruses or bacteria and I knew I could have done something to prevent it, I couldn't live with myself. If you're going to let this child out without being vaccinated I can't see you anymore because I'm responsible for the health of this child.' With that [approach], she has been far more successful. Because at some level, if you continue to see that patient, you're tacitly agreeing that it's okay to [not vaccinate]."

In 2000, Dr. Offit and colleagues created the Vaccine Education Center at Children's Hospital of Philadelphia, which provides complete, up-to-date, and reliable information about vaccines to parents and clinicians. It summarizes the purpose of each vaccine, and the relative risks and benefits in easy-to-read language. The CDC also maintains updated information about vaccines and immunizations on its web site. For his part, Dr. Offit tells parents that passing on an opportunity to vaccinate their child is not a risk-free choice. "If you choose not to get a vaccine you probably will get away with it, but you might not," he said. "You are playing a game of Russian roulette. It may not be five empty chambers and one bullet, but maybe it's 100,000 empty chambers and one bullet. There's a bullet there."

Dr. Offit reported having no relevant financial disclosures.

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Repeat pneumococcal disease may signal immunodeficiency

BY BIANCA NOGRADY
MDedge News

Recurrent invasive pneumococcal disease in children could be a signal of underlying primary immunodeficiency, according to a study published in JAMA Pediatrics.

Coen Butters, BMed, DCH, of the Royal Children's Hospital, Melbourne, wrote that, even with optimal vaccine coverage, there are still children with increased susceptibility to invasive pneumococcal disease (IPD), and this could be a potential marker of primary immunodeficiency.

They conducted a systematic review of 17 studies of 6,002 children to examine the evidence on the incidence of primary immunodeficiency in children who presented with IPD but without any other risk factors or predisposing conditions. Overall, the frequency of primary immunodeficiency in children presenting with IPD who did not have any other predisposing condition was 1%-26%.

One study of 162 children with IPD, which had an overall frequency of primary immunodeficiency of 10%, found that children older than 2 years were significantly more likely to have primary immunodeficiency than those aged under 2 (26% vs. 3%).

Primary antibody deficiency was the most commonly diagnosed immunodeficiency in these children with IPD, accounting for 71% of cases. These deficiencies presented as hypogammaglobulinemia, specific pneumococcal antibody deficiency, X-linked agammaglobulinemia, and IgG2 deficiency.

The review also included four studies that looked at the frequency of mannose-binding lectin deficiency in 1,493 children with primary IPD. Two of these studies reported a prevalence of mannose-binding lectin deficiency ranging from 31% in children aged younger than 2 years to 41% in children younger than 1 year.

Five studies looked at the rate of primary immunodeficiency in children presenting with recurrent IPD. In addition to other predisposing conditions such as sickle cell disease, cancer, and anatomical breach in the blood-brain barrier, the three studies that screened for primary immunodeficiency found rates ranging from 10% to 67%. The most common conditions were complement deficiency, pneumococcal antibody deficiency, and a single case of TLR-signaling defect.

The authors declared no conflicts.

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SOURCES: Butters C et al. JAMA Pediatr. 2019 Sep 30. doi: 10.1001/jamapediatrics.2019.3203.

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1 Victor F. Tapson. The OPTALYSE PE Trial JACC: Cardiovascular Interventions Jul 2018; 11(14): 1401-1410; DOI: 10.1016/j.jcin.2018.04.008

2 Konstantinides, MD, et al, "Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism" Journal of the American College of Cardiology; vol 69, pp.1536-1544, 2017.

Environmental scan: Drivers of philanthropy

BY THERESE BORDEN
MDedge News

Philanthropy is a driving force supporting and promoting pioneering research and programs in many fields of medicine. Charitable giving, foundation support, and grants touch the lives of millions of patients and also have an impact across all fields of medical practice. Four factors stand out as most likely to have a significant influence on philanthropy decisions in the coming years. These include advancements in technology, ability to make an impact, accountability, and the recent tax reform laws. Donors want more information and more options for giving. They want to know how their dollars are being used and the impact of their donation. Individuals donate to causes and organizations that are important to them and reflect their values. In addition, what motivates Baby Boomers and Gen Xers to give frequently differs from what factors into the giving decisions of Millennials.

CHEST INSPIRATION: Pacing the Future

Dr. Addrizzo-Harris

In 2019, Charity Navigator reported total giving to charitable organizations was $427.1 billion, 0.7% measured in current dollars over the revised total of $424.74 billion contributed in 2017.[1]

Doreen Addrizzo-Harris, MD, FCCP, Professor of Medicine, NYU School of Medicine, and Past President of CHEST Foundation, has observed these trends in philanthropy first hand. "Overall total giving has decreased by 1.7%. However, giving to foundations has increased by 7.3% during the same time period. The CHEST Foundation wants to take advantage of this change. People, particularly Millennials, want to feel more connected with the organizations that they give to. They want to know where their donations are going, and they want to have more of a personal connection with the organization or foundation."

Impact investing, transparency, and trust

As donors become more focused on results, organizations will need to demonstrate their ability to achieve short-term goals that bring them closer to accomplishing their mission and vision. This sentiment may be strongest among Millennials. Nonprofit organizations should expect an increased level of due diligence and a higher level of personal involvement by donors.[2]

Health care–related issues

Two of the top three issues identified by donors as a challenge to be addressed are related to health care, according to Fidelity Charitable. Thirty-nine percent identified "developing treatment or cures for a disease" and 33% cited "access to basic health services" as priority issues. A study by Giving USA estimated that charitable giving to healthcare organizations rose a strong 7.3% (5.5% adjusted for inflation) in 2017, but giving that year was fueled by a booming stock market and a favorable tax environment. Charitable donations to hospitals tend to reflect the economic health of the community in which the institution is located. Donations to rural hospitals in depressed communities are likely to be far less than to urban institutions in economically strong areas.[3]

Tax reform

The Tax Cuts and Jobs Act of 2017 will likely affect donations to charitable organizations in 2019. Specifically, the 2017 Tax Act doubled the standard tax deduction, thereby reducing the number of households having to itemize their deductions and eliminating many tax benefits for charitable donations. Middle-class families are expected to opt for the standard deduction while wealthier taxpayers will likely continue itemizing their deductions. As a result, some predict that donors may switch from giving annually to giving every third year so they can itemize in their giving years to get the deduction.[4]

Technology and peer-to-peer giving

Technological advances that make researching and giving easier and more convenient are likely to have a significant impact on many charitable organizations in 2019. Online donations are likely to increase as organizations make it simple to donate from mobile devices, social media platforms, and their websites. Although charitable organizations will continue to directly ask individuals for a donation, many are expanding their efforts to include online social campaigns that leverage peer-to-peer giving. Other technological advancements likely to affect donations in the future include the ability for organizations to incorporate contactless payment programs and blockchain technology. [5]

Generational differences in giving

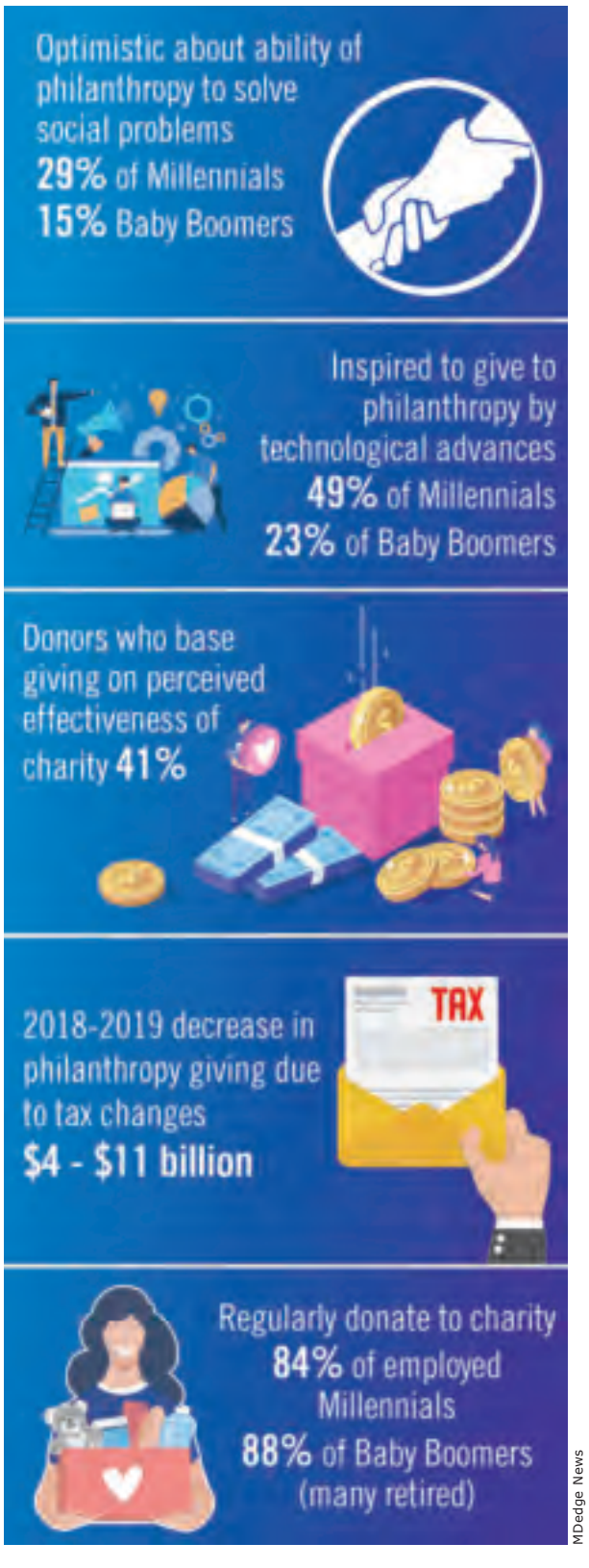
Although the trends identified above are likely to affect the decision to give in 2019, there are some meaningful differences in how different generations embrace these changes. Technological advances, the rise of alternative forms of giving, and increased opportunities to connect with peers about giving influence Millennials significantly more than Baby Boomers. Millennials are more likely to say that they give to make a meaningful difference while Boomers are likely to say that giving is part of their values. Millennials also are more likely to say their giving is more spontaneous, while Boomers say their giving is more planned. As many as 49% of Millennials cite technological advances influencing their giving, compared with only 23% of Baby Boomers. This trend continues for the rise of alternative forms of giving (32% of Millennials, compared with 14% of Boomers) and increased opportunities to connect with peers about giving (30%, compared with 11%).

Twenty-nine percent of Millennials are very optimistic about philanthropy's ability to solve the issues most important to them, compared with only 15% of Baby Boomers. Both generations prioritize challenges related to health, hunger, and the environment.[6]

Today, foundations need to focus on impact, not just education programs or scholarships. New tech-driven trends in giving, such as the emergence of digital peer-to-peer giving and crowdfunding campaigns, make it possible to tap into high-volume, small-amount donations. To recruit new donors, organizations will need to target their messages based on the audience segment.

Dr. Addrizzo-Harris notes that the CHEST Foundation is responding to these trends. "The

Continued on page 27



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YUPELRI®
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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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Continued from page 24

CHEST Foundation is working to become more patient- and community-friendly and to reach out beyond their physician member pool. The Foundation allows patients, their families, and physicians to feel like they are actively involved with programs that include community health projects, patient education material, or fundraising events. Recently, we have changed our giving platform to be more technology-friendly. We also have expanded the ways a potential donor can give by now including text and expanded online giving sites.

She continued, "We are also actively revamping our website to enhance our communication with our physician members, patients, their families, and their communities by making disease-specific sites that help with empowering the patient and the physician to have access to expert care. We have expanded our fundraising events to include patients and their families and interested nonphysician members in the communities. Many of our events focus on families who want to help other patients have better access to care. Events such as the Feldman Family Poker event this past March and the upcoming *Golden Era of EP* event, an evening celebrating Erin Popovich and the launch of the new endowment bearing her name, highlight ways that the CHEST Foundation is working with families to promote disease awareness and help enhance access to care.

Dr. Addrizzo-Harris concluded, "We hope that by more effectively engaging our donors, we will increase total giving as they will feel a personal connection to the CHEST Foundation."

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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Critical Care Commentary

Nutrition support during adult critical illness

BY JAYSHIL J. PATEL MD; AND TODD RICE, MD, FCCP

Many critically ill patients you care for cannot maintain volitional oral intake. Therefore, nutrition support, through enteral or parenteral routes, remains a cornerstone in ensuring our critically ill patients receive substrates like glucose and protein. To understand the supportive role of nutrition during critical illness, let's identify and contextualize the different phases of critical illness.

Dr. Patel

Dr. Rice

Phases of critical illness

The European Society of Parenteral and Enteral Nutrition's (ESPEN) 2018 critical care nutrition guideline incorporates stages of critical illness in making nutrition recommendations (Singer P et al. *Clin Nutr.* 2019;38:48-79). The first week of critical illness is the acute phase and hallmarked by catabolism and metabolic and hemodynamic instability. The late phase is thereafter and hallmarked by rehabilitation and anabolism or chronic critical illness. The acute phase is further divided into early (days 1-2) and late acute phase (days 3-7). The time-points are arbitrary and merely serve as placeholders. An objective marker to distinguish phases does not exist, and transition periods will be different for each patient.

Acute phase

Critical illness defining conditions like circulatory shock, respiratory failure, and trauma are stressors and lead to two key acute phase perturbations that nutrition may have a role in altering:

The first is hypercatabolism. Critical illness defining conditions activate neuroendocrine, inflammatory/immune, adipokine, and GI tract hormone pathways that increase serum glucagon, cortisol, and catecholamines to promote glycogenolysis, gluconeogenesis, insulin resistance, protein catabolism, and restricted/impaired anabolism.

The second is gut dysfunction. During health, there is cross-talk signaling that occurs between commensal bacteria, epithelium, and the immune system, which maintains gut barrier functions, achieved, for example, by promoting tight junction protein production. Acute critical illness pathophysiology loosens epithelial tight junctions, and the gut barrier is breached, creating an opportunity for downstream migration of pancreatic enzymes and cytokines. Furthermore, the microbiome morphs into a virulent pathobiome, which induces gut-derived inflammation.

When, where, and how much should we feed critically ill patients?

Since the acute phase of critical illness begins a series of events leading to negative energy balance and gut dysfunction, you might find early nutrition provision intuitive. Indeed, the 2016 ASPEN/SCCM and 2018 ESPEN critical care nutrition guidelines recommend early (within 24-48 hours of ICU admission) enteral nutrition (EN), delivered into the stomach, for all critically ill patients unable to maintain volitional intake. Meta-analyses of randomized controlled trials (RCT) conducted between 1979 and 2013 show early EN reduces both mortality and infectious complications, compared with no early nutrition (McClave SA et al. *JPEN.* 2016;40:159-211).

RCT level data do not show superiority of EN over parenteral nutrition (PN). Nonetheless, early EN is recommended over PN because it maintains epithelial barrier function and supports immunity.

What is the optimal nutrition dose? The 2016 ASPEN/SCCM guideline recommends getting to >80% estimated energy goal within 48-72 hours in patients with high nutrition risk while the 2018 ESPEN guideline suggests maintaining a hypocaloric, or not exceeding 70% of prescribed energy goal, during the early acute phase. The recommendation is based on meta-analyses of RCTs conducted between 2011 and 2017, which shows no mortality difference between hypocaloric and isocaloric nutrition.

Biologically plausible rationale for starting hypocaloric, as opposed to full dose nutrition, during the acute phase of critical illness includes: (a) the acute phase represents a period of hemodynamic instability and mitochondrial dysfunction, and full-dose EN may lead to feeding intolerance and lack of substrate utilization, respectively; (b) in those with risk factors (like pre-existing malnutrition), starting full dose nutrition may lead to refeeding syndrome; and (c) endogenous glucose production occurs during the acute phase, and full dose nutrition may worsen hyperglycemia.

Therefore, during the early acute phase of critical illness, hypocaloric feeding using an isosmotic formula, with a slow up-titration to goal rate thereafter, while monitoring for feeding intolerance and refeeding syndrome is a reasonable starting point.

What is the role of parenteral nutrition in critical illness?

PN can be exclusive or supplemental (in a patient receiving EN). Historically, providers may have been reluctant to utilize PN for fear of infectious morbidity; however, contemporary pragmatic-design RCTs demonstrate safety with exclusive PN (Harvey SE et al. *N Engl J Med.* 2014;371:1673-84). When your patient has a contraindication for EN or does not tolerate it despite a trial of small bowel feeding, meta-analyses have shown a mortality benefit of early exclusive PN in malnourished patients, as compared with no nutrition (Braunschweig C et al. *Am J Clin Nutr.* 2001;74:534-42).

As for supplemental PN (SPN), the 2016 ASPEN/SCCM guideline does not recommend it until day 7 in all critically ill patients, while the 2018 ESPEN guideline recommends its use on a case-by-case basis. Since, two trials inform SPN use. The EAT-ICU trial showed no difference in 6-month physical function between EN group and early-goal-directed nutrition group, which included SPN to achieve estimated energy requirement during the first week of critical illness (Allingstrup MJ et al. I*ntensive Care Med.* 2017;43:1637-47). The TOP-UP trial compared EN alone with EN plus SPN in nutritionally high risk patients (ie, those who stand to have more complications as a result of undernutrition) and found those with a BMI < 25 kg/m^2 and those with a NUTRIC score >5 who received supplemental PN atop EN had improved 30-day mortality, as compared with EN alone (Wischmeyer P et al. *Crit Care.* 2017;21:142). Mortality was a secondary outcome, and further study of supplemental PN in nutritionally high-risk patients is warranted. Until further data are available, supplemental PN should probably be restricted during the acute phase of critical illness.

Protein may be the important substrate

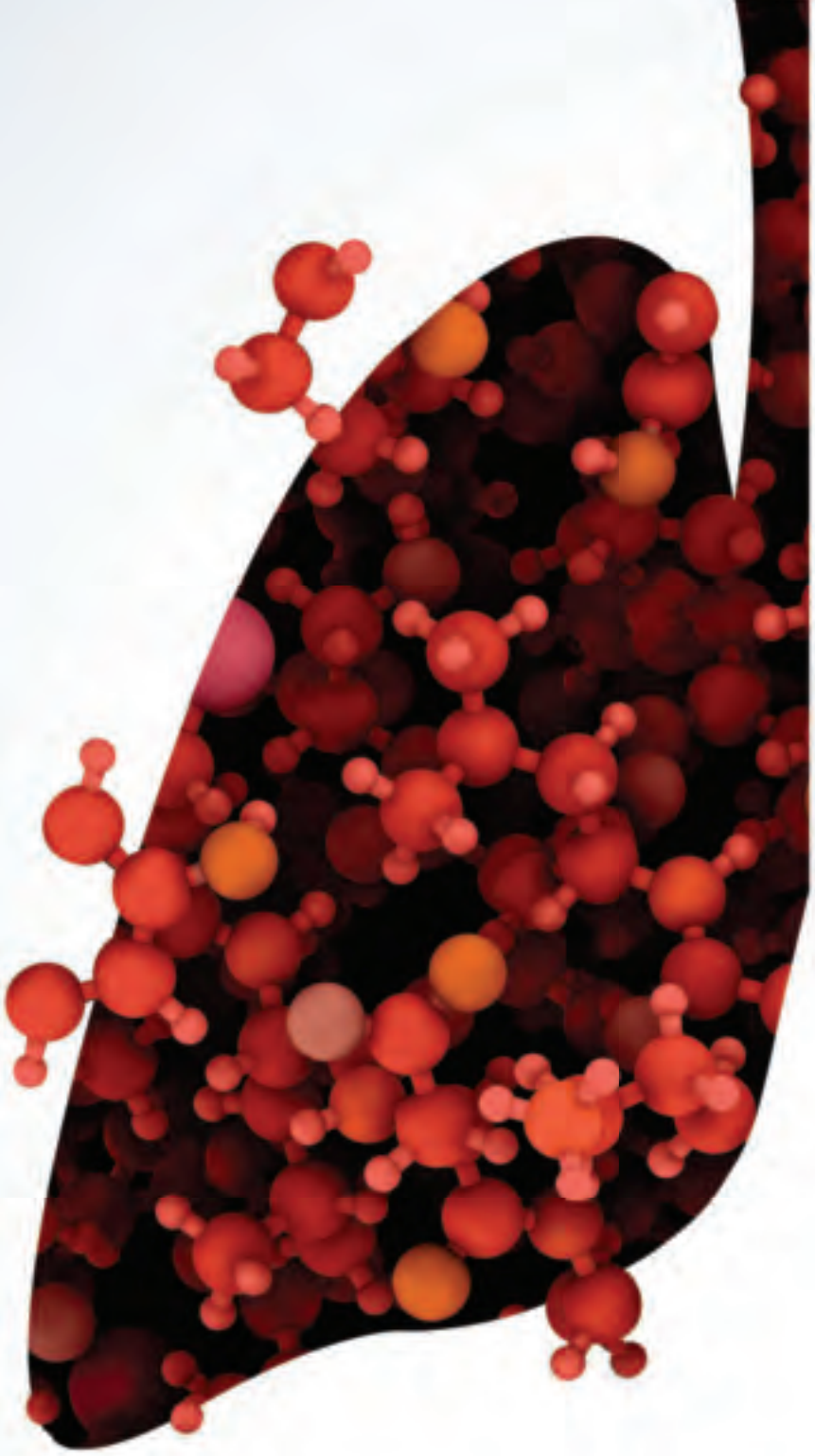
Proteolysis is the rule during critical illness, and amino acids are liberated from skeletal muscle breakdown. Using ultrasound, Puthucheary et al found a 17.7% reduction in rectus femoris cross-sectional area in 63 critically ill adults and identified muscle cellular infiltration at ICU day 10, suggesting critical illness leads to quantitative and qualitative muscle defects (Puthucheary Z et al. *JAMA*. 2013;15:1591-1600).

Since survivorship from critical illness is increasing, acquired loss of muscle mass may contribute to post-ICU physical functioning impairments. Thus, protein may be the most important substrate to deliver during critical illness. The 2016 ASPEN/SCCM guideline recommends 1.2 – 2.0 g/kg actual body weight (ABW)/day in nonobese critically ill patients.

Unfortunately, the optimal protein dose and the timing of intake are unknown. Observational studies suggest benefit with lower and higher doses, which creates equipoise for protein dose. The signal may be lost in heterogeneity, and observational data suggest higher protein dose may benefit patients with high nutritional risk. In terms of timing, one observational study found lower (<0.8 g/kg/d) protein dose before day 3 followed by higher (>0.8 g/kg/d) dose thereafter was associated with mortality benefit (Koekkoek WAC et al. *Clin Nutr.* 2019;38:883-890).

Until stronger data are available to guide optimal protein dose and timing, it is reasonable to observe the 2016 ASPEN/SCCM guideline protein recommendation of at least 1.2 g/kg/day. The 2018 ESPEN guideline recommends a similar dose of 1.3 g/kg/day.

NUTRITION // *continued on page 31*



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News from the Board of Regents: Highlights of ongoing successes

BY NEIL FREEDMAN, MD, FCCP

CHEST leadership recently met for its fall quarterly face-to-face meeting prior to CHEST 2019 in New Orleans. Like all CHEST board meetings, the agenda was packed with important topics and a great deal of meaningful discussion. I left the meeting more energized about CHEST and its current and future offerings for our membership. Below are a few highlights from the meeting.

The meeting opened with an update from outgoing CHEST President Clayton Cowl, MD, MS, FCCP. He highlighted some of the organization's major achievements over the past year, including: Confirming and signing a new contract with our EVP/CEO Robert Musacchio, PhD; hiring a new Chief Learning Officer, a new Editor in Chief for the *CHEST*® journal, and a new Chief Legal Counsel; and expansion of the international strategy with CHEST Congress Bangkok and a CHEST Regional meeting in Athens with plans for CHEST Congress 2020 in Bologna, Italy. In addition, CHEST convened a Digital Strategy Task Force, which made recommendations to improve how members, patients, and staff interact with our organization.

Dr. Musacchio reviewed some additional organizational accomplishments and areas of focus for the future. These included redefining the One CHEST operating model and a continued emphasis on international business development with plans for CHEST Congress 2020 in Italy, in addition to the exploration of future meetings in Singapore and the Philippines. CHEST remains dedicated to innovation by crafting new experiences for our members, including new games, virtual patient tours, and enduring activities and products. Many of these experiences were highlighted and on display at the recent CHEST annual meeting, including a pulmonary-focused "escape room" and mobile "pop-up" simulation experiences. Kudos to CHEST 2019 Program Chair Bill Kelly, MD, FCCP, who led an incredible team of volunteer members in crafting the best collective member experience to date!

Dr. Freedman

• Next up was a report out from the Governance Committee, which is composed of members of both the College Board of Regents (BOR) and Foundation Board of Trustees (BOT) and is responsible for the overall health of both boards and ensuring that the boards are consistently performing at a high level. Committee Chair, and CHEST Immediate Past President John Studdard, MD, FCCP, led the Committee presentation and discussion, which predominantly consisted of the delivery of slates for 2019-20 Board of Trustees (BOT) and Board of Regents (BOR) for Board approval. The new BOR-approved members are Douglas Arenberg, MD, FCCP; Sandhya Khurana, MD, FCCP; Lisa Moores, MD, FCCP; Michael Nelson, MD, FCCP; and Alexander Niven, MD, FCCP. Also, newly slated seats approved for the BOR: Ian Nathanson, MD, FCCP (CHEST Foundation President-Elect),and Angel Coz Yataco, MD, FCCP (Vice-Chair, Council of NetWorks).

New BOT-approved members are Roozehra Khan, DO, FCCP; Jill Popovich; and Burton Lesnick, MD, FCCP, with newly slated seats approved by the BOT that include Stephanie Levine, MD, FCCP (CHEST President); and Sai Haranath, MBBS, MPH, FCCP (Chair, Executive Committee of the Council of Global Governors).

In addition, David Schulman, MD, MPH, FCCP, and Robert De Marco, MD, FCCP, were elected as President-Designate of the BOR and BOT, respectively; both will serve their presidential terms beginning in October 2021.

Several others presented to the Board to review the past year's progress, future plans, and potential barriers to success:

• John Howington, MD, FCCP, Chair of the Finance Committee, updated the board on the financial health of the organization; in brief, CHEST had a very strong financial report for the past year based on strong expense management by our executive leadership team.

• The Council of Global Governors continues to see expansion in our international membership, though a potential ongoing barrier to future engagement will be developing an efficient mode of communication between the Global Governors and the international members they represent. Discussion around using the expertise within the Digital Strategy Task Force was offered as one method to improve international member communication and engagement.

• Alex Niven, MD, FCCP, Chair of the Education Committee, reported that they received an unprecedented 130 nominations for membership during this past election cycles and identified new members with exceptional credentials for the 2019-20 term. The Education Committee has expanded three of its subcommittees to better include and engage these individuals in ongoing education projects.

• Matt Miles, MD, FCCP, presented on behalf of the Training and Transitions Committee that continues to see increased engagement from trainees and training programs. This year's meeting in New Orleans had an increased number of trainee submissions, as well as a greater percentage of submissions that were accepted for presentation at the meeting. The committee will continue to evolve their strategy for engaging trainees and early career professionals.

• Christopher Hergott, MD, FCCP, Chair of the Membership Committee, reviewed several strategies and recommendations to expand our membership offerings and improve the value that we bring to our all of our members.

Finally, it was time to say thank you and farewell to out our outgoing Board members. The following Board of Regents members were recognized for their many years of service to CHEST: Jack Buckley, MD, FCCP; John Studdard, MD, FCCP; David Zielinski, MD, FCCP; and Burt Lesnick, MD, FCCP.

Mark J. Rosen, MD, Master FCCP Endowment

When most think of Mark J. Rosen, MD, Master FCCP, so many words come to mind: master educator, astute and caring clinician, researcher, mentor, leader. We recall his generosity, kindness, honesty, brilliance, and sense of humor.

Mark loved CHEST. He gave so much to the organization and was happy to do so. He was one of the rare Past Presidents who contributed even more after his presidency than during or before. Mark left an enormous footprint on CHEST's educational programs, including the CHEST Annual Meeting, Pulmonary Board Review, and SEEK. He was instrumental in building our international educational programs and a key player in empowering our Chinese colleagues in establishing pulmonary fellowships in their country. Much of what we have all accomplished at CHEST and in pulmonary medicine is directly related to the wonderful mentors we have had in the organization, and Mark was certainly one of the most prominent.

Mark introduced many of us to so many friends and mentors. He especially did this for hundreds of trainees and junior faculty throughout his career. What made him most happy was seeing his trainees and mentees succeed – Mark was THE example of an outstanding mentor. After his passing, and in recognition

Dr. Mark J. Rosen

of his work that can and will live on, the CHEST Foundation has established an endowment with a major focus that truly honors Mark's most memorable traits – the Rosen International Scholarship Fund.

Mark always believed the core strength of the college was education. The CHEST Foundation is endowing the Rosen International Scholarship and raising $100,000 to support deserving international clinicians. This endowed fund will directly support international CHEST members' travel to the CHEST Annual Meeting affording CHEST's world-class educational and mentorship opportunities to members who could not otherwise attend.

To support the Mark J. Rosen, MD, Master FCCP Endowment, his legacy, and international CHEST members, visit https://tinyurl.com/wf7zeq6.

Nutrition // *continued from page 28*

Future research and summary

Many questions remain unanswered and present opportunities for future research. Priorities for critical care nutrition research include studying the impact of combined nutrition and exercise in the acute and late phases of critical illness and identifying best tools to differentiate responses to caloric and protein intake.

In summary, critical illness has acute and late phases. The acute phase is a hypercatabolic state leading to negative energy and nitrogen balance and gut dysfunction. Take-home points for nutrition support in the acute phase of critical illness are:

1. It is reasonable to start early hypocaloric EN with an isosmotic formula with slow up-titration over the first week of critical illness while monitoring for refeeding syndrome and feeding intolerance.
2. Use exclusive PN in ICU patients with pre-existing malnutrition when EN is contraindicated or not tolerated.
3. Supplemental PN should probably be restricted during the acute phase of critical illness.
4. Optimal protein dose and timing are unknown. It is reasonable to start with at least 1.2 g/kg ABW/day in non-obese patients.

Dr. Patel is with the Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin.

Dr. Rice is with the Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Vanderbilt University, Nashville, Tennessee.

NAMDRC legislative initiatives take shape

BY PHIL PORTE
Executive Director, NAMDRC

Two priorities of NAMDRC have moved into the formal congressional arena. The issues focus on access to pulmonary rehabilitation and CMS's move to include home mechanical ventilation in competitive bidding.

Pulmonary Rehabilitation – The Problem: One of the major concerns to CMS and Congress is the fact that different payment methodologies for the same service result in different payment amounts dependent upon the actual site of service. To address the phenomenon of hospitals purchasing certain physician practices to game the payment system, Congress included in the 2015 Budget Act a provision that would remove incentives for such hospital purchases by stating that new hospital outpatient services must be within 250 yards of the main hospital campus in order to receive payment based on the hospital outpatient prospective payment system methodology. If a hospital opens such services beyond that 250-yard threshold, the hospital would be reimbursed at the physician fee schedule amount for the same service. Likewise, if an off campus program moved its grandfathered location because of expansion, loss of lease, etc, the physician fee schedule would again kick in.

For pulmonary rehabilitation services, this is extremely problematic and is tying the hands of hospitals providing this service. The physician fee schedule payment for pulmonary rehabilitation is less than $30 for 1 hour of service, and it is, therefore, not surprising that the service is simply not provided in physician offices. In fact, Medicare data show that all physician specialties bill less than $1M for code **G0424**, and we believe that most of that is likely billing error. Pulmonologists bill less than $500K for code **G0424**, and putting that number in context, the entire Medicare program is approaching $700B in outlays.

Pulmonary Rehabilitation – The Solution: As a solution to this problem, HR 4838 has been introduced in the House of Representatives. There is no specific reference to pulmonary rehabilitation in the bill as our approach is based not only on substance but political considerations, as well. Using CMS' own acknowledgment of "unintended consequences," this legislation would exempt all CPT® codes from the restrictions imposed by Section 603 of the 2015 Budget Act when the physician billings for that code are under $2M for the most recent year for which data are available. CMS has signaled to us that such a limitation would apply only to pulmonary and cardiac rehab services, but others may be affected, as well. By putting a dollar limit rather than identifying a specific service for such a "carve out," it is a more politically viable approach.


Mr. Porte

Bills such as this rarely see the light of day; however, such provisions are often attached to larger, more substantive bills. For nearly 2 decades, the common legislative vehicle for such provisions is a larger Medicare bill, often including "must pass Medicare extender" provisions that are slated to expire on a particular date. Our goal is to include HR 4838 in such a package of extenders some time between now and the end of this Congress in 2020.

Home Mechanical Ventilation – The Problem: CMS has proposed inclusion of home mechanical ventilation in competitive bidding for durable medical equipment. Such a regulatory proposal is fraught with downside risk, most notably that such a policy would follow the history of liquid oxygen. Liquid 02 has virtually disappeared from the marketplace since it was included in competitive bidding as suppliers simply refused to provide liquid oxygen systems as their own bidding dropped the price to prohibitively low levels. Also, because there is a statutory requirement that such payment be made on the basis of "frequent and substantial servicing," and that stipulation could trigger wide variations in actual bidding because some states require involvement of respiratory therapists in such services, while others do not.

It is critical to understand that the driving force behind all of this is the reality that CMS' own coverage policies for home mechanical ventilation are seriously flawed and outdated, creating perverse incentives for physicians to order easily accessible systems rather than clinically appropriate ones. NAMDRC and its sister societies have been pushing CMS to revise those policies with no success.

Home Mechanical Ventilation – The Solution: Our solution is twofold. HR 4945 bill was introduced on November 1, 2019. First, the proposed legislation would create a blanket exemption for home mechanical ventilation from competitive bidding. Second, it requires CMS to convene a technical expert panel to craft up-to-date policies for home mechanical ventilation.

The political strategy here is slightly different. While passage of the bill is certainly our first choice, we believe that introduction of the bill is a red flag signal to CMS for the need to revise its coverage policies as those policies are the root cause of the growth of home mechanical ventilation outlays.

This month in the journal *CHEST*®

Editor's Picks

BY PETER J. MAZZONE, MD, MPH, FCCP
Editor in Chief

Editorials

Pulmonary Embolism Cardiac Arrest: Thrombolysis During Cardiopulmonary Resuscitation and Improved Survival.
By Drs. B. W. Bottiger and W. A. Wetsch.

Interstitial Lung Abnormalities: A Word of Caution.
By Drs. V. Tzilas and D. Bouros.

Original Research

Thrombolysis During Resuscitation for Out-of-Hospital Cardiac Arrest Caused by Pulmonary Embolism Increases 30-Day Survival: Findings From the French National Cardiac Arrest Registry.
By Dr. F. Javaudin, et al.

Interstitial Lung Abnormalities and Lung Cancer Risk in the National Lung Screening Trial.
By Dr. S-A. Whittaker Brown, et al.

Commentary

Publishing a Clinical Research Manuscript: Guidance for Early-Career Researchers With a Focus on Pulmonary and Critical Care Medicine.
By Dr. E. M. Viglianti, et al.

CHEST 2020 honor lectures and award nominations

Each year, CHEST honors physicians and others who are making significant or meritorious contributions to chest medicine. All honorees are recognized for advancing work in specific areas of chest medicine, mentorship, and training, furthering the work of CHEST, and more.

If you believe you have a colleague who should be recognized for their distinguished work, please submit a nomination. Those selected for an annual award and honor lecture will be featured at CHEST 2020 in Chicago.

Deadline: Monday, January 6, 2020

Questions? Please contact Emily Petraglia, Manager, Volunteer Engagement by email: epetraglia@chestnet.org.

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An update on the current standard for ultrasound education in fellowship

BY LEWIS SATTERWHITE, MD, FCCP; KALEB VEIT, DO; AND ARIEL SHILOH, MD, FCCP

Point-of-care ultrasound (POCUS) is an essential part of ICU care. It has been demonstrated to improve patient safety and outcomes through procedural guidance (Brass P, et al. *Cochrane Database Syst Rev*. 2015 Jan 9;1:CD006962) and aid in accurate and timely diagnosis of cardiopulmonary failure (Lichtenstein DA, Mezière GA. *Chest*. 2008 Jul;134[1]:117-25). Due in part to increasing affordability and portability of ultrasound technologies, the use of POCUS has become seemingly ubiquitous and will continue to increase in coming years. According to expert groups representing 12 critical care societies worldwide, general critical care ultrasound and basic critical care echocardiography should be mandatory training for ICU physicians (Expert Round Table on Ultrasound in ICU. *Intensive Care Med*. 2011 Jul;37[7]:1077-83).

Currently, POCUS is not universally taught to pulmonary and critical care fellows (PCCM); and when training does exist, curriculums are not standardized. This is in part due to the broadly worded requirements set forth from the ACGME for pulmonary disease and critical care medicine. The totality of ACGME common program requirements as it regards to ultrasound training are as follows: 1. "Fellows must demonstrate competence in procedural and technical skills, including ... use of ultrasound techniques to perform thoracentesis and place intravascular and intracavitary tubes and catheters"; and 2. "Fellows must demonstrate knowledge of imaging techniques commonly employed in the evaluation of patients with pulmonary disease or critical illness, including the use of ultrasound" (*ACGME Program Requirements for Graduate Medical Education in Pulmonary Disease and Critical Care Medicine*).

In comparison, recently updated ACGME common program requirements for ultrasound in emergency medicine and anesthesiology residencies are robust and detailed. Requirements for anesthesia residency training include: "... competency in using surface ultrasound ... and transthoracic echocardiography to guide the performance of invasive procedures and to evaluate organ function and pathology ... understanding the principles of ultrasound, including the physics of ultrasound transmission, ultrasound transducer construction, and transducer selection for specific applications, to include being able to obtain images with an understanding of limitations and artifacts ... obtaining standard views of the heart and inferior vena cava with transthoracic echocardiography allowing the evaluation of myocardial function, estimation of central venous pressure, and gross pericardial/cardiac pathology (eg, large pericardial effusion) ... using transthoracic ultrasound for the detection of pneumothorax and pleural effusion ... using surface ultrasound to guide vascular access (both central and peripheral) ... describing techniques, views, and findings in standard language" (*ACGME Program Requirements for Graduate Medical Education In Anesthesiology*).

Herein lies a stark contrast in what is required of programs that train physicians to care for unstable patients and the critically ill. Current requirements leave graduates of PCCM training programs vulnerable to completing ACGME milestones without being adequately prepared to evaluate patients in a modern ICU setting. Hospitals credentialing committees expect PCCM graduates to be suitably trained in ultrasound. Regrettably, there is no assurance that is true, or standardized, with current PCCM fellowship training requirements.

There is not a national standard for

competency assessment or requirements for credentialing in POCUS for critical care physicians at this time. However, multiple national and international critical care societies, including CHEST, have consensus statements and recommendations outlining the areas of competence expected in critical care ultrasound (Mayo PH, et al. *CHEST*. 2009 Apr;135[4];1050-60, Expert Round Table on Ultrasound in ICU. *Intensive Care Med*. 2011 Jul;37(7):1077-83). The PCCM ACGME requirements should be updated to reflect such recommendations, thereby placing greater emphasis on ultrasound teaching requirements and standardized curriculums. Despite the current ACGME program requirements, it is incumbent upon critical care training programs to provide competency-based education of this now "standard of care" technology.

Barriers to universal POCUS training exist. Fellowship programs may lack trained, ultrasound confident faculty, time, and funding to successfully develop and sustain an ultrasound curriculum (Eisen LA, et al. *Crit Care Med.* 2010;38[10]:1978-83; Patrawalla P, et al. *J Intensive Care Med*. 2019 Feb 12:[Epub ahead of print]).

Although access to adequate quality and quantity of ultrasound machines is less often a problem than in the past, many institutions lack archival and image review software that allows for quality assurance of image acquisition, and some still may not have a faculty member with expertise and ability to champion the cause.

In attempts to mitigate the local faculty gaps, national and regional solutions have been developed for ultrasonography education. CHEST has educated more than 1,400 learners in the Ultrasound Essentials course since 2013. Also, grassroots efforts have led to the development of courses specifically designed to teach incoming PCCM fellows. Using a collaborative and cost-effective model, these regional programs pool faculty and experts in the field to train multiple fellowship programs simultaneously. The first of these was created over a decade ago in New York City (Patrawalla P, et al. *J Intensive Care Med*. 2019 Feb 12:[Epub ahead of print].)

Currently, there are at least four regional annual ultrasound courses directed at teaching PCCM fellows. These courses are typically held over multiple days and encompass the basics of critical care ultrasound, including vascular, thoracic, abdominal, cardiac, and procedural imaging. By estimation, these four courses provide a basic ultrasonography education to approximately two-thirds of first year pulmonary and critical care fellows in the United States. In addition to training fellows, these programs also serve as a platform for the development of local faculty experts, so that training can continue at their institutions.

Introductory courses are highly effective (Dinh VA, et al. *Crit Care Res Pract*. 2015 Aug 5:675041; Patrawalla P, et al. *J Intensive Care Med.* 2019 Feb 12: [Epub ahead of print]), but ongoing education, assessment, and quality assurance is required to achieve sustained competence. Ideally, training in POCUS should entail a dedicated, intensive introduction to the competencies of critical care ultrasound (such as the above regional courses or CHEST ultrasound courses), followed by a formal curriculum within the PCCM fellowship programs.

This curriculum should afford the trainee exposure to critically ill patients in an environment with adequate ultrasound equipment and a method to record studies. The trainee then interprets the acquired studies in clinical context. Preferably, the program will afford the trainee real-time quality assurance for image acquisition and interpretation by a program champion. Quality assurance can be provided on site or remotely using fixed interval review sessions.

Lastly, the program should have internal milestones to evaluate when a trainee has reached competency to perform these tasks independently. The completion of training should include a letter to any future employee attesting to the trainee's acquisition of these skills and ability to apply them safely while caring for the critically ill. This robust education is occurring in many centers across the country. PCCM fellowship programs owe it to their trainees, and patients, that competency-based critical care ultrasound training is robust, standardized, and supported.

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