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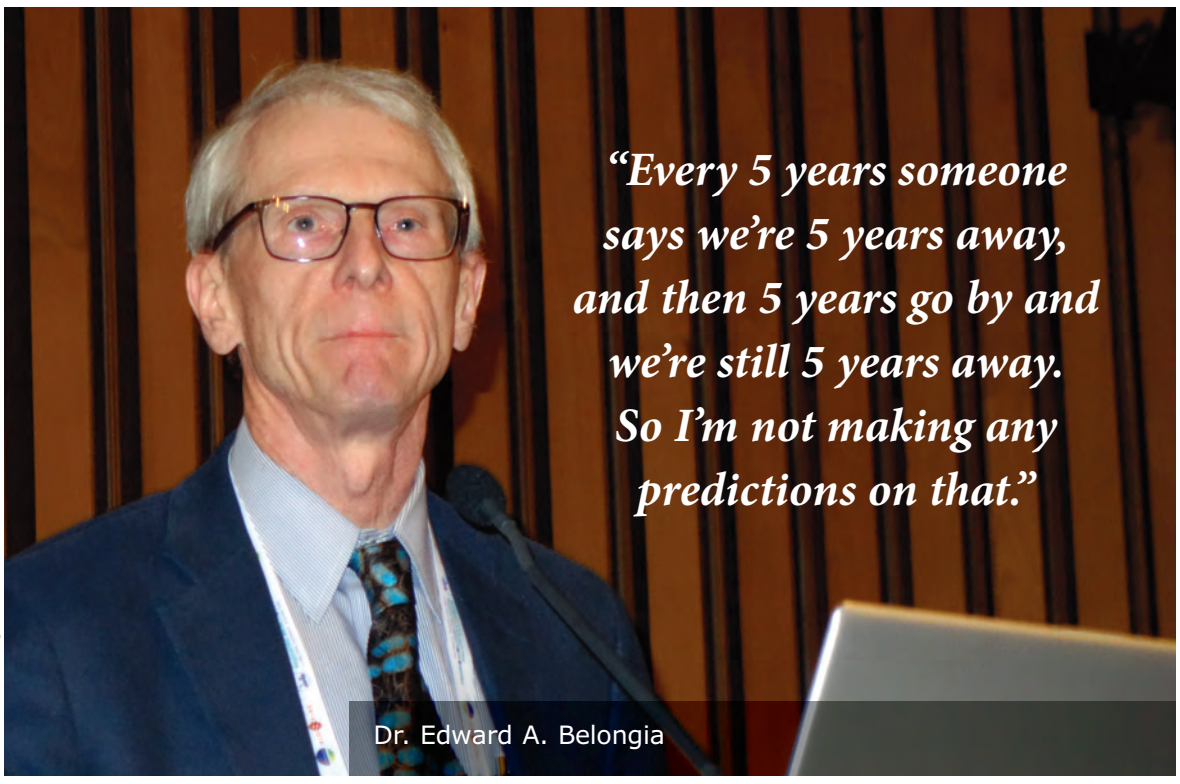

Bruce Jancin/MDedge News

Dr. Edward A. Belongia

Obstacles remain in the way of developing better flu vaccines

BY BRUCE JANCIN
MDedge News

LJUBLJANA, SLOVENIA – An improved, more reliably effective influenza vaccine may not be on the horizon in the near future.

That was a key cautionary message provided by vaccine expert Edward A. Belongia, MD, at the annual meeting of the European Society for Paediatric Infectious Diseases.

The effectiveness of seasonal influenza vaccine varies from 10% to 60% year by year, leaving enormous room for improvement. But many obstacles exist to developing a more consistent and reliably effective version of the seasonal influenza vaccine. And the lofty goal of creating a universal vaccine is even more ambitious, although the National Institute of Allergy and Infectious Diseases has declared it to be a top priority and mapped out a strategic plan for getting there (J Infect Dis. 2018 Jul 2;218[3]:347-54).

"Ultimately the Holy Grail is a universal flu vaccine that would provide pan-A and pan-B protection that would last for more than 1 year, with protection against avian and pandemic viruses, and would work for both children and adults. We are nowhere near that. Every 5 years someone says we're 5 years away, and then 5 years go by and we're still 5 years away. So I'm not making any predictions on that," said Dr. Belongia, director of the Center for Clinical Epide-

FLU VACCINES // *continued on page 7*

OSA prevalence in North and South America estimated at 170 million

BY DOUG BRUNK
MDedge News

The estimated prevalence of obstructive sleep apnea in North and South America stands at 170 million, results from a novel epidemiologic analysis showed.

"I would not have thought that there are 170 million people in the Americas with clinically important sleep apnea based on our conservative estimates," the study's first author, Atul Malhotra, MD, FCCP, said in an interview in advance of the annual meeting of the Associated Professional Sleep Societies. "Even if we restrict the conversation to moderate to severe sleep apnea, we still see 81 million people afflicted in the Americas alone. We have recently estimated almost 1 billion patients afflicted with OSA worldwide."

In an effort to estimate the Americas' prevalence of adult OSA using existing data from epidemiologic studies, Dr. Malhotra, director of sleep medicine at the University of California, San Diego, senior author Adam V. Benjafield, PhD, and their colleagues contacted authors of important analyses on the topic following an

OSA // *continued on page 7*

INSIDE HIGHLIGHT

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Sleep Strategies

Restless Legs Syndrome

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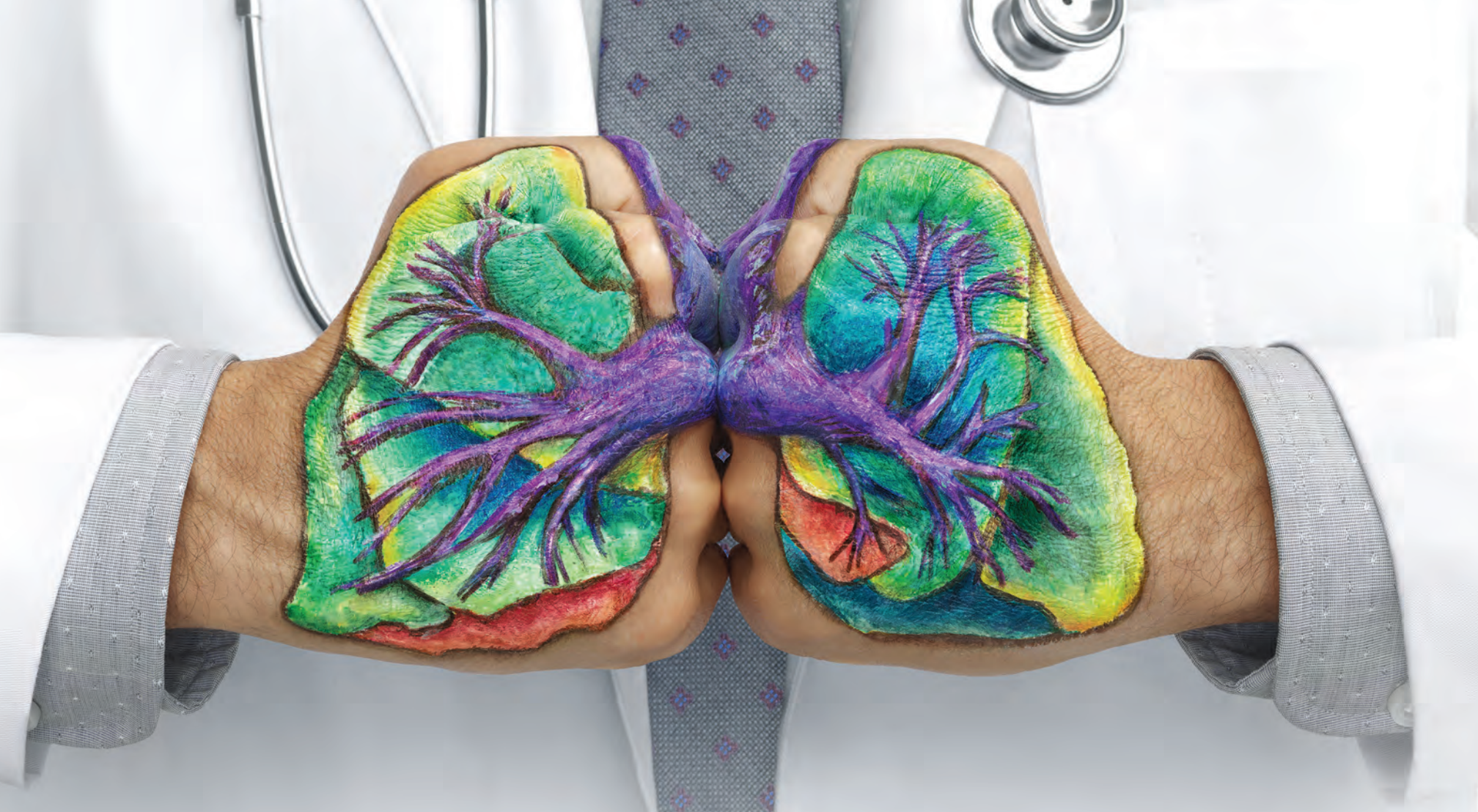

Indication

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

Select Important Safety Information

Elevated liver enzymes: Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3× ULN (3.7%) compared with placebo patients (0.8%). In some cases, these have been associated with concomitant elevations in bilirubin. No Esbriet-related cases of liver transplant or death due to liver failure have been reported. However, combined elevations of transaminases and bilirubin without evidence of obstruction is considered an important predictor of severe liver injury that could lead to death or the need for a transplant.

Measure ALT, AST, and bilirubin levels prior to initiating Esbriet, then monthly for the first 6 months, and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with placebo patients (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, compared with 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications 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 reductions of Esbriet are 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 37,000 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 using 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. October 2017. **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. 2016.

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]**

†In clinical trials, serious adverse reactions, including elevated liver enzymes, 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

COPD rates reflect current smoking prevalence

BY STEVE CIMINO
MDedge News

Chronic obstructive pulmonary disease (COPD) prevalence among adults is strongly correlated with their state's current smoking prevalence, according to a Centers for Disease Control and Prevention analysis of respondents to a behavioral risk factor survey.

"Population-based strategies for smoking prevention and control have the potential to decrease the prevalence of COPD in the United States," wrote Anne G. Wheaton, PhD, of the CDC's National Center for Chronic Disease Prevention and Health Promotion and coauthors. The study was published in the Morbidity and Mortality Weekly Report.

Dr. Wheaton and her fellow researchers analyzed data from

418,378 adult respondents to the 2017 Behavioral Risk Factor Surveillance System survey. Responses came from all 50 states and Washington, D.C.; respondents who had smoked less than 100 lifetime cigarettes were categorized as "never smoked," while those who had smoked at least 100 cigarettes but no longer smoked were categorized as "former smokers." Anyone who had smoked at least 100 cigarettes and currently smoked was categorized as a "current smoker."

The age-adjusted prevalence of COPD among U.S. adults was 6.2% (95% confidence interval, 6.0%-6.3%) in 2017. Current cigarette smokers had a prevalence of 15.2% (95% CI, 14.7%-15.7%); this dipped to 7.6% (95% CI, 7.3%-8.0%) among former smokers and 2.8% (95% CI, 2.7%-2.9%) among adults who had never smoked. Patterns were visible within states: Current smokers had a state-level prevalence of COPD that was strongly correlated with state-level current smoking prevalence (Pearson correlation coefficient, 0.69; *P* less than .001). State-level COPD prevalence among former smokers (Pearson correlation coefficient, 0.71; *P* less than .001) and those who never smoked (Pearson correlation coefficient, 0.64; *P* less than .001) were also strongly correlated with the current smoking prevalence, indicating secondhand smoke as a risk factor for COPD.

"Population-based strategies for smoking prevention and control have the potential to decrease the prevalence of COPD in the United States."

The findings on populations at higher risk for COPD were not unexpected. The higher COPD prevalences observed among women, older adults, American Indians/Alaska Natives, adults with less education, those with a history of asthma, and those residing in rural areas were consistent with results from previous studies.

Smoking prevention policies including tobacco product price increases, mass media antismoking campaigns, comprehensive smoke-free laws, and barrier-free access to evidence-based cessation interventions all could attack COPD prevalence in the United States, the report suggests. In addition, policies to help protect nonsmokers from secondhand smoke exposure can also make an impact on COPD prevalence.

The coauthors acknowledged the study's limitations, including relying on self-reporting for both COPD and smoking status. They also noted that there was no way to measure exposure to secondhand smoke, other indoor or outdoor air pollutants, or respiratory infection history, "all of which might contribute to COPD risk."

No conflicts of interest were reported.

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SOURCE: Wheaton AG et al. MMWR Morb Mortal Wkly Rep. 2019 Jun 21;68(24):533-8.

AMA names recipients of Reimagining Residency initiative

BY LUCAS FRANKI
MDedge News

The American Medical Association has announced the final eight recipients of the Reimagining Residency initiative, who will receive a total of $14.4 million to support residency innovation projects led by medical schools, residency programs, and health systems.

"After establishing a framework for creating the medical schools of the future, the AMA is now supporting innovation projects that will better align residency training with the evolving needs of patients and communities," AMA CEO and Executive Vice President James L. Madara, MD, stated.

The projects include curricular innovations to address workforce shortages and address social determinants of health. Other projects will be developed within the framework of innovations and concepts developed and implemented in medical schools over the past 6 years by the AMA's consortium.

The projects were chosen through a competitive grant process by an advisory panel made up of leading experts in medical education, and selection was based on how well each program met the goals of the initiative

Each of the following projects will receive $1.8 million over 5 years:

- California Oregon Medical Partnership to Address Disparities in Rural Education and Health – Oregon Health & Science University, Portland, and the University of California, Davis
- Fully Integrated Readiness for Service Training: Enhancing the Continuum from Medical School to Residency to Practice – University of North Carolina at Chapel Hill
- NYU Transition to Residency Advantage – New York University
- Promotion in Place: Enhancing Trainee Well-Being and Patient Care Through Time-Variable Graduate Medical Education – Partners HealthCare System, Massachusetts General Hospital, and Brigham and Women's Hospital, Boston
- Reimagining Residency: Ensuring Readiness for Practice Through Growing Interprofessional Partnerships to Advance Care and Education – Maine Medical Center, Portland
- Residency Training to Effectively Address Social Determinants of Health: Applying a Curricular Framework Across Four Primary Care Specialties – Montefiore Health System, New York
- The Graduate Medical Training "Laboratory": An Innovative Program to Generate, Implement, and Evaluate Interventions to Improve Resident Burnout and Clinical Skill – Johns Hopkins University, Baltimore; Stanford (Calif.) University; and the University of Alabama at Birmingham
- The GOL2D Project (Goals of Life and Learning Delineated): Collaboration Across Academic Health Systems to Better Align GME with Learner, Patient, and Societal Needs – Vanderbilt University, Nashville, Tenn., and the University of Mississippi, Jackson.

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VIEW ON THE NEWS

David A. Schulman, MD, FCCP, comments: It is refreshing to see additional attention (and funding) being deployed to helping our residents see more of what medicine has to offer. Studies show that the vast majority of people entering medical school continue to do so with the primary goal of helping the public, and yet burnout rates for postgraduate trainees climb year after year, related to nonclinical aspects of the job (like documentation), long work hours, the growing debt associated with pursuit of medical training, and the emotionally stressful task of treating patients with severe and premorbid medical conditions. There's much ongoing discussion about maintaining the well-being of physicians-in-training, but I would opine that projects like the ones being funded by the AMA, that allow us to be creative in what and how we teach these doctors, are far more likely to rekindle the residents' flame of enthusiasm for medicine than free food or social gatherings.

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

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Flu vaccines against H3N2 remain less effective for younger children // *continued from page 1*

miology and Population Health at the Marshfield (Wisc.) Clinic Research Institute, which is part of the U.S. Influenza Vaccine Effectiveness Network.

One of the big problems in creating a more effective flu vaccine, particularly for children, is the H3N2 virus subtype. Dr. Belongia was first author of a systematic review and meta-analysis of studies of more than a dozen recent flu seasons showing that although vaccine effectiveness against H3N2 varied widely from year to year, it was consistently lower than against influenza type B and H1N1 (Lancet Infect Dis. 2016 Aug;16[8]:942-51).

And that's especially true in children and adolescents. Notably, in the 2014-2015 U.S. flu season, vaccine effectiveness against H3N2 in children aged 6 months to 8 years was low at 23%, but shockingly lower at a mere 7% in the 9- to 17-year-olds. Whereas in the 2017-2018 season, vaccine effectiveness against H3N2 in the 9- to 17-year-olds jumped to 46% while remaining low but consistent at 22% in the younger children.

"We see a very different age pattern here for the older children compared to the younger children, and quite frankly we don't really understand what's doing this," said Dr. Belongia.

What is well understood, however, is that the problematic performance of influenza vaccines when it comes to protecting against H3N2 is a complicated matter stemming from three sources: the virus itself; the current egg-based vaccine manufacturing methodology, which is now 7 decades old; and host factors.

That troublesome H3N2 virus

Antigenic evolution of the H3N2 virus occurs at a 5- to 6-fold higher rate than for influenza B virus and roughly 17-fold faster than for H1N1. That high mutation rate makes for a moving target that's a real problem when trying to keep a vaccine current. Also, the globular head of the virus is prone to glycosylation, which enables the virus to evade immune detection.

Vaccine-related factors

It's likely that the availability of the flu vaccine for the upcoming 2019-2020 season is going to be delayed because of late selection of the strains for inclusion. The World Health Organization ordinarily selects strains for vaccines for the Northern Hemisphere in February, giving vaccine manufacturers 6-8 months to produce their vaccines and ship them in time for administration from September through November. This year, however, the WHO delayed selection of the H3N2 component until March because of the high level of antigenic and genetic diversity of circulating strains.

"This hasn't happened since 2003 – it's a very rare occurrence – but it does increase the potential that there's going to be a delay in the availability of the vaccine in the fall," he explained.

Eventually, the WHO selected a new clade 3C.3a virus called A/Kansas/14/2017 for the 2019-2020 vaccine. It should cover the circulating strains of H3N2 "reasonably well," according to the physician.

Another issue: H3N2 has become adapted to the mammalian environment, so growing the virus in eggs introduces strong selection pressure for mutations leading to reduced vaccine effectiveness. Yet only two flu vaccines licensed in the United States are manufactured without eggs: Flucelvax, marketed by Seqirus for patients aged 4 years and up, and Sanofi's Flublok, which is licensed for individuals who are 18 years of age or older. Studies are underway looking at the relative effectiveness of egg-based versus cell culture–?>manufactured flu vaccines in real-world settings.

Host factors

Hemagglutinin imprinting, sometimes referred to as "original antigenic sin," is a decades-old concept whereby early childhood exposure to influenza viruses shapes future vaccine response.

"It suggests there could be some birth cohort effects in vaccine responsiveness, depending on what was circulating in the first 2-3 years after birth. It would complicate vaccine strategy quite a bit if you had to have different strategies for different birth cohorts," Dr. Belongia observed.

Another host factor issue is the controversial topic of negative interference stemming from repeated vaccinations. It's unclear how important this is in the real world, because studies have been inconsistent. Reassuringly, Dr. Belongia and coworkers found no association between prior-season influenza vaccination and diminished vaccine effectiveness in 3,369 U.S. children aged 2-17 years studied during the 2013-2014 through 2015-2016 flu seasons (JAMA Netw Open. 2018 Oct 5;1[6]:e183742. doi: 10.1001/jamanetworkopen.2018.3742).

"We found no suggestion at all of a problem with being vaccinated two seasons in a row," according to Dr. Belongia.

How to build a better influenza vaccine for children

"I would say that, even before we get to a universal vaccine, the next generation of flu vaccines that are more effective are not going to be manufactured using eggs, although we're not real close to that. But I think that's eventually where we're going," he said.

"I think it's going to take a systems biology approach in order to really understand the adaptive immune response to infection and vaccination in early life. That means a much more detailed understanding of what is underlying the imprinting mechanisms and what is the adaptive response to repeated vaccination and infection. I think this is going to take prospective infant cohort studies; the National Institutes of Health is funding some that will begin within the next year," Dr. Belongia added.

Dr. Belongia reported having no financial conflicts regarding his presentation.

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OSA prevalence in the United States estimated at 54 million // *continued from page 1*

exhaustive review of the literature. For countries where no measurement had been made, they used publicly available data to obtain estimates of age, sex, race, and body mass index. Next, they developed an algorithm to match countries without prevalence estimates with countries from which OSA epidemiologic studies exist. "The situation was complicated given the variable age of the existing studies, the differences in technology used (e.g., nasal pressure vs. thermistor), the changing scoring criteria, and other sources of variability," the researchers wrote in their abstract.

Dr. Malhotra reported on data from 38 of 40 countries in the Americas. Drawing from American Academy of Sleep Medicine 2012 criteria and using what they characterized as a "somewhat conservative" approach, the researchers estimated the prevalence of adult OSA in the Americas to be 170 million, or 37% of the population. In addition, they estimate that 81 million adults, or 18% of the population, suffer from moderate to severe OSA based on an apnea hypopnea index of 15 or more per hour. The countries with the greatest burden of OSA are the United States (54 million), Brazil (49 million), and Colombia (11 million).

Dr. Atul Malhotra

"The findings will hopefully help to raise awareness about the disease but also encourage a strategic conversation regarding how best to address this large burden," Dr. Malhotra said. "We are unaware of prior efforts to estimate OSA prevalence on a large scale."

He acknowledged certain limitations of the study, including that the methods, equipment, definitions, and criteria used in existing studies in the medical literature varied widely. "We did our best to harmonize these methods across studies but obviously we can't change the equipment that was used in previous studies," he said. "Thus, we view our findings as an estimate requiring further efforts to corroborate."

The research stemmed from an academic/industry partnership with ResMed, which provided a donation the UCSD Sleep Medicine Center. Dr. Malhotra reported having no financial disclosures. Dr. Benjafield is an employee of ResMed, a medical equipment company that specializes in sleep-related breathing devices.

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SOURCE: Malhotra A et al. SLEEP 2019, Abstract 0477.

Cost of physician burnout estimated at $4.6 billion per year

BY RICHARD FRANKI
MDedge News

Physician burnout costs the U.S. health care system approximately $4.6 billion a year in physician turnover and reduced productivity, according to the results of a cost-consequence analysis.

In 2015, the burnout-attributable cost per physician was $7,600 – an estimate occupying the conservative middle ground between the $3,700 and $11,000 extremes produced by the study's mathematical model.

"Traditionally, the case for ameliorating physician burnout has been made primarily on ethical grounds." This study, believed to be the first to look at the system-wide costs of burnout, "provides tools to evaluate the economic dimension of this problem," wrote Shasha Han, MS, of the National University of Singapore and her associates in Annals of Internal Medicine.

Individual burnout-attributable costs were higher for physicians in the younger age group (less than 55 years) in all three specialty categories: $7,100 versus $5,900 for those aged at least 55 years among primary care physicians, $10,800 versus $9,100 for surgical specialists, and $7,800 versus $6,100 for other specialists, the investigators reported.

The mathematical model used in the study focused on two productivity metrics related to burnout – cost associated with physician replacement and lost income from unfilled physician positions. "Estimated turnover costs were generally higher than costs of reduced productivity across all" the various segments of age and specialty, Ms. Han and associates wrote.

"Burnout is a problem that extends beyond physicians to nurses and other health care staff. Future work holistically investigating the costs associated with burnout in health care organizations would be valuable. Studies focusing on differences in burnout-attributable costs across provider segments other than the ones investigated in this study, including academic versus private settings, or across a finer segmentation of physician specialties also might be fruitful," they wrote.

One investigator has received grants from the American Medical Association Accelerating Change in Medical Education Consortium, the Physicians Foundation, and the National Institutes of Health. Another received a startup grant from the National University of Singapore. Ms. Han said that she had no financial conflicts to disclose. All of the investigators' disclosures are available online.

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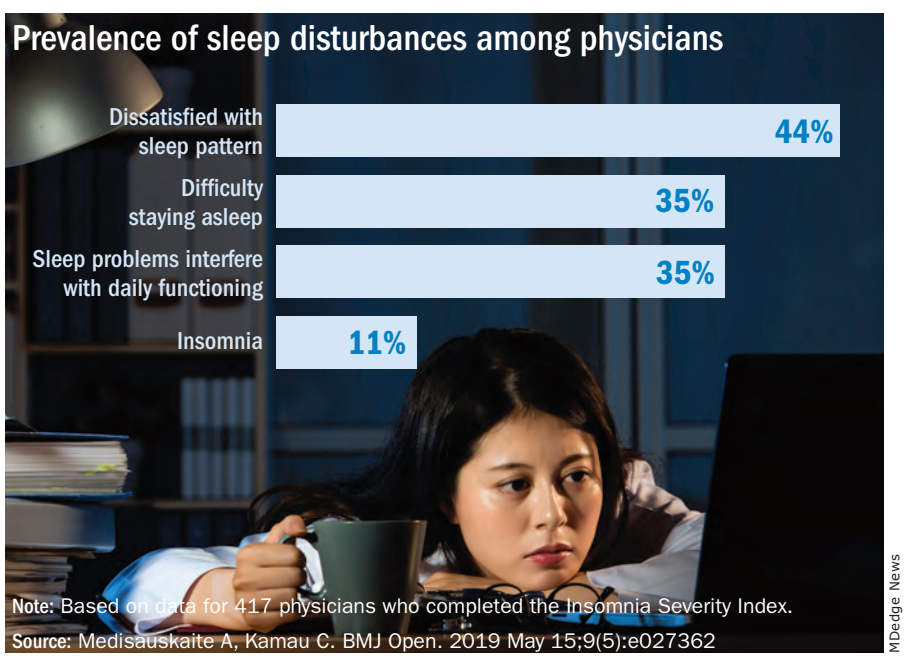
SOURCE: Han S et al. Ann Intern Med. 2019 May 28. doi: 10.7326/M18-1422.



Vaping among teens shot up from 2017 to 2018

BY RICHARD FRANKI
MDedge News

Vaping among teens aged 16-19 years rose significantly in the United States and Canada from 2017 to 2018 but did not change in England, according to data from national cross-sectional surveys.

The prevalence of vaping in the past 30 days rose from 11% to 16% in the United States and from 8% to 14.6% in Canada, while use in England showed an nonsignificant increase of 8.7% to 8.9%, David Hammond, PhD, of the University of Waterloo (Canada) and associates said in the BMJ.

Embedded in those U.S. and Canadian increases is the recent evolution of the vaping market brought about by "the growth of JUUL e-cigarettes and similar products [that use] benzoic acid and nicotine salt technology to deliver higher concentrations of nicotine than conventional e-cigarettes," they explained.

In England, the JUUL system is limited to less than half the nicotine concentration, at 20 mg/mL, compared with more than 50 mg/mL in the United States and Canada, and it was not available at all types of retail outlets at the time of the surveys. That situation changed in March 2019, when the company expanded to convenience stores, the investigators noted.

In the United States, JUUL was the second-most popular product among past–30-day vapers who had a usual brand in 2017, with 9% reporting use. In 2018, JUUL was the most popular brand and use was up to 28%. In Canada, the brand was not among the top five in 2017, but was third in 2018 at 10% in those who reported vaping in the past 30 days. The leading Canadian brand in 2018 was Smok, which released a nicotine-salt version in March of 2018, Dr. Hammond and associates reported.

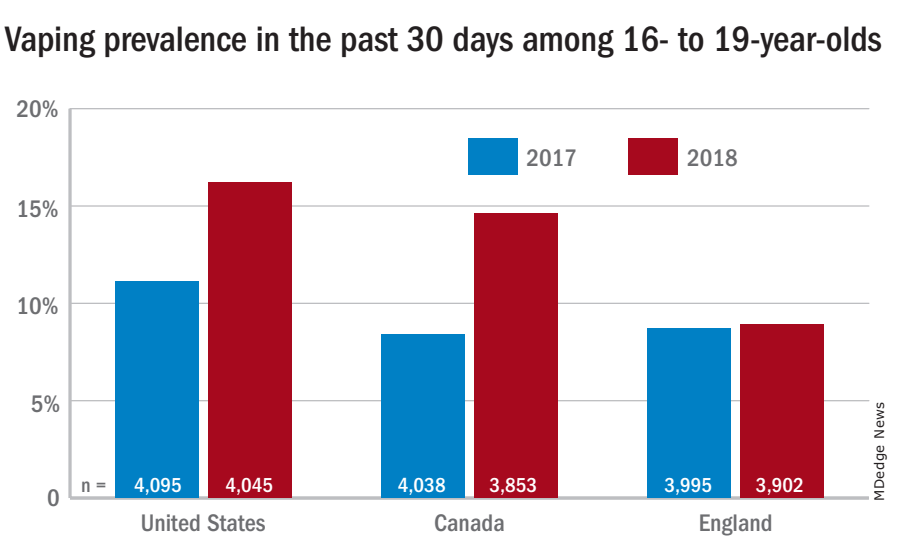
"Before 2018, there was relatively little evidence of regular vaping among adolescents that might be indicative of nicotine addiction; however, the emergence of JUUL and nicotine salt–based products might signal a change," they wrote.

The International Tobacco Control Policy Evaluation Project's Youth Tobacco and Vaping Survey was conducted online in each country in two waves – July to August 2017 and August to September 2018 – with a sample size of approximately 12,000 for each.

The study was funded by the U.S. National Institutes of Health. Dr. Hammond is supported by a Canadian Institutes of Health Research–Public Health Agency of Canada applied public health research chair. The investigators said that they had no other financial disclosures to report, but several have served as paid witnesses in legal challenges against tobacco companies.

rfranki@mdedge.com

SOURCE: Hammond D et al. BMJ 2019 Jun 19. doi: 10.1136/bmj.l2219.



Note: Based on data from the International Tobacco Control Policy Evaluation Project's Youth Tobacco and Vaping Survey, conducted in Jul-Aug 2017 and Aug-Sept 2018.

Source: BMJ 2019 Jun 19;365:l2219

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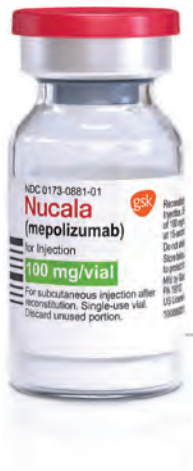

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Nintedanib cut lung function decline in interstitial lung disease caused by systemic sclerosis

BY MICHELE G. SULLIVAN
MDedge News

DALLAS – Nintedanib, a tyrosine kinase inhibitor, decreased by 44% the annual rate of lung function decline among patients with interstitial lung disease associated with systemic sclerosis, a year-long study has found.

In a placebo-controlled 52-week trial, forced vital capacity (FVC) in patients who took nintedanib (Ofev) declined by a mean of 52 mL – significantly less than the mean 93-mL decline seen among those who were given placebo, Oliver Distler, MD, said at the annual meeting of the American Thoracic Society.

"These are people in their mid-40s and -50s. They have a long time to go. If there is an annual preservation of lung function by 40%, if you have that every year, it becomes very surely clinically significant. A decline in FVC is also a good surrogate marker of mortality in interstitial lung disease associated with systemic sclerosis."

"These are people in their mid-40s and -50s," said Dr. Distler of the University of Zürich. "They have a long time to go. If there is an annual preservation of lung function by 40%, if you have that every year, it becomes very surely clinically significant. A decline in FVC is also a good surrogate marker of mortality in interstitial lung disease associated with systemic sclerosis. Assuming the effects are ongoing above the 1 year we looked at, then indeed these results are clinically important."

The study was simultaneously published in the New England Journal of Medicine. Nintedanib is already approved for idiopathic pulmonary fibrosis. But some data suggest that it also exerts antifibrotic and anti-inflammatory effects in animal models of systemic sclerosis and inflammatory lung disease (ILD). SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) investigated the molecule's use in patients with ILD associated with systemic sclerosis.

Conducted in 32 countries, SENSCIS comprised 576 patients with the disorder, whose sclerosis affected at least 10% of their lungs. They were assigned to 52 weeks of either placebo or 150 mg nintedanib twice weekly. However, patients stayed on their blinded treatment until the last patient enrolled had finished the year of treatment; some patients took the drug for 100 weeks, Dr. Distler said.

The primary endpoint was annual rate of decline in the forced vital capacity (FEV). Secondary endpoints included changes of the modified Rodnan skin score and in the total score on the St. George's Respiratory Questionnaire.

Patients were a mean of 54 years old, with a mean disease duration of about 3 years. About half had diffuse cutaneous systemic sclerosis; the sclerosis was limited in the remainder. The mean extent of lung fibrosis was about 36%. Half were taking mycophenolate at baseline, which was allowed as background treatment, along with up to 10 mg/day of prednisone. Any patient who experienced clinically significant lung function deterioration could receive additional therapy at the investigator's discretion.

The mean baseline FEV for these patients was 72.5% of predicted value. The mean diffusing capacity of the lungs for carbon monoxide was 53% of expected capacity.

Most patients completed the study (80% of the active group and 89% of the placebo group). The mean drug exposure duration was 10 months in the active group and 11 in the placebo group.

Improvement began early in treatment, with the efficacy curves separating by week 12 and continuing to diverge. After 52 weeks of therapy, the annual rate of change was 41 mL less in the active group than in the placebo group (–54.4 mL vs. –93.3 mL). The mean adjusted absolute change from baseline was –54.6 mL in the active group and –101 mL in the placebo at week 52. Significantly fewer patients taking nintedanib also lost more than 10% of FVC by week 52 (16.7% vs. 18%).

The St. George's Respiratory Questionnaire score improved about one point in the active group and declined about one point in the placebo group.

Dr. Oliver Distler

Nintedanib was equally effective across a number of subgroups, including those divided by sex, age, and race. Antitopoisomerase antibodies and so-called antitopoisomerase I antibody status did not affect nintedanib's action. Nintedanib also significantly improved scores on the Health Assessment Questionnaire Without Disability Index and Dyspnea.

More patients in the active group than on placebo discontinued treatment because of a serious adverse event (16% vs. 8.7%). The most common of these were diarrhea (75.7% vs. 31%), nausea (31.6% vs. 13.5%), and vomiting (24.7% vs.10.4%).

Skin ulcers occurred in about 18% of each group. Patients in the active group were significantly more likely to develop elevated alanine and aspartate aminotransferase of up to three times normal levels (4.9% vs. 0.7%).

The trial had some limitations. Patients with clinically significant pulmonary hypertension were excluded so the data cannot be applied to patients with this comorbidity.

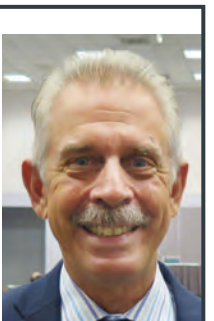
The nintedanib and placebo groups showed no difference in patient-reported outcomes and health-related quality of life. No treatment effect was observed with respect to skin fibrosis, as assessed with the use of the modified Rodnan skin score

In addition, treatment did not significantly affect mortality rates. Over the treatment period, 10 patients in the nintedanib group and 9 in the placebo group died (3.5% vs. 3.1%). In addition, researchers stated, "The lower rate of decline in FVC in the nintedanib group was not accompanied by a benefit with respect to health-related quality of life. ... An uncontrolled open-label extension study (NCT03313180) is ongoing and will provide long-term data on nintedanib therapy in patients with ILD associated with systemic sclerosis."

The study was sponsored by Boehringer Ingelheim. Dr. Distler was the primary investigator on the trial.

msullivan@mdedge.com

SOURCE: Distler O et al. ATS 2019, Abstract A7360.



Daniel R. Ouellette, MD, FCCP, comments: She had traveled a long way to come and see me. The young pharmacist in her 30s had struggled for several years to balance her symptoms of systemic sclerosis with the demands of a busy profession. Upon learning that she might have lung disease, she had sought a referral to a tertiary center specialty clinic in the geographically diffuse medical system where we both worked. Thus began regular visits with pulmonary function tests, CT scans, and discussions about immunosuppressive regimens, interspersed with friendly chit-chat. Over time, her interstitial lung disease steadily worsened. She died years ago waiting for her transplant. It is good to think that in nintedanib we might have a medicine that would slow progression of this terrible disease. We need more research to confirm these findings and to learn if other important outcomes are improved as well.

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Cannabis vaping among teens tied to tobacco use

BY HEIDI SPLETE
MDedge News

One in 10 high school students has used an e-cigarette device to vaporize (vape) cannabis and that practice is associated with cigar, waterpipe, and e-cigarette use, findings from a survey of nearly 3,000 adolescents have shown.

"Although the prevalence of e-cigarette use among youth has increased dramatically in the past decade, little epidemiologic data exist on the prevalence of using e-cigarette devices or other specialised devices to vaporise ('vape') cannabis in the form of hash oil, tetrahydrocannabinol (THC) wax or oil, or dried cannabis buds or leaves," wrote Sarah D. Kowitt, PhD, of the University of North Carolina, Chapel Hill, and colleagues. "This is surprising given that (1) cannabis (also referred to as marijuana) and e-cigarettes are the most commonly used substances by adolescents in the USA, (2) evidence exists that adolescents dual use both tobacco e-cigarettes and cannabis, and (3) longitudinal research suggests that use of e-cigarettes is associated with progression to use of cannabis."

In a study published in BMJ Open, the researchers used data from the 2017 North Carolina Youth Tobacco Survey, a school-based survey of students in grades 6-12. The study population included 2,835 adolescents in grades 9-12.

Overall, 9.6% of students reported ever vaping cannabis. In multivariate analysis, cannabis vaping was significantly more likely among adolescents who reported using e-cigarettes (adjusted odds ratio 3.18), cigars (aOR 3.76), or water pipes (aOR 2.32) in the past 30 days, compared with peers who didn't use tobacco.

6okean/Getty Images

The researchers found no significant association between smokeless tobacco use or traditional cigarette use in the past 30 days and vaping cannabis.

In a bivariate analysis, vaping cannabis was significantly more common among males vs. females (11% vs. 8.2%) and among non-Hispanic white students (11.3%), Hispanic students (10.5%), and other non-Hispanic students (11.8%) compared with non-Hispanic black students (5.0%).

In addition, prevalence of cannabis vaping increased with grade level, from 4.7% of 9th graders to 15.5% of 12th graders.

The health impacts of vaping cannabis are not well researched, but the researchers note that among the potential safety issues are earlier initiation of tobacco or cannabis use, concomitant tobacco and cannabis use, increased frequency of use or misuse of tobacco or cannabis, or increased potency of cannabis.

The results of the study were limited by several factors including the use of data only from the state of North Carolina, the lack of data on frequency or current vaping cannabis behavior, lack of data on specific products, and lack of data on whether teens used specialized devices or e-cigarettes for cannabis vaping. However, the findings are consistent with studies on prevalence of cannabis vaping in other states such as Connecticut and California. "No studies to our knowledge have examined how adolescents who vape cannabis use other specific tobacco products (i.e., cigarettes, cigars, waterpipe, smokeless tobacco)," the researchers wrote.

The findings confirm that a large number of adolescents who use tobacco products have vaped cannabis as well, and this growing public health issue "is likely to affect and be affected by tobacco control and cannabis policies in states and at the federal level in the USA," the researchers concluded.

"Increased research investigating how youth use e-cigarette devices for other purposes beyond vaping nicotine, like the current study, is needed," they added.

The study was supported in part by the National Cancer Institute and the Food and Drug Administration's Center for Tobacco Products. The researchers had no financial conflicts to disclose.

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SOURCE: Kowitt SD et al. BMJ Open. 2019 Jun 13. doi: 10.1136/bmjopen-2018-028535.

Eosinophil-guided therapy reduces corticosteroid use in COPD

BY BIANCA NOGRADY
MDedge News

Using eosinophil levels to guide steroid treatment in patients with chronic obstructive pulmonary disease (COPD) was found to be noninferior to standard treatment in terms of the number of days out of hospital and alive, new research has found.

Writing in the Lancet Respiratory Medicine, researchers reported the outcomes of a multicenter, controlled, open-label trial comparing eosinophil-guided and standard therapy with systemic corticosteroids in 318 patients with COPD.

Pradeesh Sivapalan, MD, of the respiratory medicine section of Herlev and Gentofte Hospital at the University of Copenhagen, and coauthors wrote that eosinophilic inflammation had been seen in 20%-40% of patients with acute exacerbations of COPD. Patients with higher eosinophilic blood counts were at increased risk of acute exacerbations but were also more likely to benefit from corticosteroid treatment.

In the eosinophil-guided therapy arm of the study, 159 patients received 80 mg of intravenous methylprednisolone on day 1, then from the second day were treated with 37.5 mg of prednisolone oral tablet daily – up to 4 days – only on days when their blood eosinophil count was at least 0.3 x 10^9 cells/L. In the control arm, 159 patients also received 80 mg of intravenous methylprednisolone on day 1, followed by 37.5 mg of prednisolone tablets daily for 4 days.

After 14 days, there were no significant differences between the two groups for mean days alive and out of hospital.

There were 12 more cases of readmission with COPD, including three fatalities, in the eosinophil-guided group within the first month. However the authors said these differences were not statistically significant, but "because the study was not powered to detect differences in this absolute risk range, we cannot rule out that this was an actual harm effect from the interventional strategy."

The eosinophil-guided therapy group did show more than a 50% reduction in the median duration of systemic corticosteroid therapy, which was 2 days in the eosinophil-guided group, compared with 5 days in the control group (*P* less than .0001), and the differences between the two groups remained significant at days 30 and 90.

"The tested strategy was successful in reducing the exposure to systemic corticosteroids, but we cannot exclude the possibility that a more aggressive algorithm, such as a single dose of systemic corticosteroid, might have been more effective," the authors wrote.

At the 90-day follow-up, there were no differences in the number of infections requiring antibiotic treatment, nor in dyspepsia, ulcer complications, or initiation of new proton-pump inhibitor treatment.

The study was supported by the Danish Regions Medical Fund and the Danish Council for Independent Research. Two authors declared personal fees from pharmaceutical companies outside the submitted work. No other conflicts were declared.

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SOURCE: Sivapalan P et al. Lancet Respir Med. 2019 May 20. doi: 10.1016/S2213-2600(19)30176-6.

Peanut desensitization comes at cost of anaphylaxis

BY HEIDI SPLETE
MDedge News

Oral immunotherapy reduced sensitivity to peanuts in allergic individuals, but at the cost of increased risk of anaphylaxis and other reactions, based on a meta-analysis from more than 1,000 patients published in the Lancet.

In the Peanut Allergen Immunotherapy, Clarifying the Evidence (PACE) systematic review and meta-analysis, Derek K. Chu, MD, of McMaster University, Hamilton, Ont., and colleagues reviewed 12 trials conducted between 2011 and 2018 with a total of 1,041 patients (median age, 9 years).

Overall, the risk of anaphylaxis was significantly higher among children who received oral immunotherapy, compared with no therapy (risk ratio, 3.12) as was anaphylaxis frequency (incidence rate ratio, 2.72) and use of epinephrine (RR, 2.21).

In addition, oral immunotherapy increased serious adverse events, compared with no therapy (RR, 1.92). Nonanaphylactic reactions also went up among oral immunotherapy patients, with increased risk for vomiting (RR, 1.79), angioedema (RR, 2.25), upper respiratory tract reactions (RR, 1.36), and lower respiratory tract infections (RR, 1.55).

Quality of life scores were not significantly different between patients who did and did not receive oral immunotherapy, the researchers noted.

The oral immunotherapy consisted of defatted, lightly roasted peanut flour in 10 studies, and a combination of peanut paste, peanut extract, or ground and defatted peanut in the other studies.

The oral immunotherapy did induce desensitization to peanuts in support of earlier studies including the subcutaneous immunotherapy trial, but "this outcome does not translate into achieving the clinical and patient-desired aim of less allergic reactions and anaphylaxis," Dr. Chu and associates wrote.

However, "rather than take the view that these data denounce current research in oral immunotherapy as not successful, we instead suggest that this research has reached an important milestone in mechanistic but not clinical efficacy. From a clinical or biological perspective, the apparently paradoxical desensitization versus longitudinal clinical findings show the lability and unreliability of allergen thresholds identified during oral food challenges because patients often unpredictably reacted to previously tolerated doses outside of clinic," they emphasized.

The findings were limited by several factors including the small sample size, compared with similar studies for asthma or cardiovascular conditions, and by incomplete or inconsistent data reporting, the researchers noted. However, the results are the most comprehensive to date, and support the need for food allergy treatments with better safety profiles, using peanut allergy immunotherapy as a model for other food allergies.

Dr. Chu and two other authors reported being investigators on a federally funded ongoing peanut oral immunotherapy trial. Two authors reported receiving a variety of grants from organizations such as the National Institutes of Health; the American Academy of Allergy, Asthma, & Immunology; or pharmaceutical companies.

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SOURCE: Chu DK et al. Lancet. 2019 Jun 1;393:2222-32.

COPD exacerbations associated with poor sleep quality

BY AMY KARON
MDedge News

FROM THE JOURNAL *CHEST*® ▪ Poor subjective sleep quality was associated with subsequent symptomatic exacerbations of chronic obstructive pulmonary disease in an 18-month prospective study of 480 patients.

"Poor sleep quality in COPD has previously been associated with reduced health-related quality of life and reduced physical activity during the day," wrote Matthew Shorofsky, MD, of McGill University, Montreal, and associates. Their report is in CHEST. "However, to our knowledge, this is the first population-based longitudinal study evaluating exacerbation risk in relation to subjective sleep disturbances and assessing previously diagnosed and undiagnosed COPD."

The study included participants enrolled in the Canadian Respiratory Research Network and the Canadian Cohort Obstructive Lung Disease (CanCOLD) study who had COPD, available baseline PSQI scores, and 18 months of follow-up data. The PSQI includes 19 questions on sleep quality, latency, duration, efficiency, disturbances, use of sleep medications, and daytime dysfunction. Total score ranges between 0 and 21, and a score above 5 is considered poor sleep. Online patient surveys and quarterly phone interviews were used to track symptom-based exacerbations (at least 48 hours of increased dyspnea, sputum volume, or sputum purulence) and event-based exacerbations (a symptom-based exacerbation plus the use of antibiotics or corticosteroids or health services).

marcociannarel/Thinkstock

At baseline, 203 patients met the PSQI threshold for poor sleep quality. During follow-up, 185 patients had at least one COPD exacerbation. Poor sleep at baseline was significantly more prevalent among patients with symptoms-based COPD exacerbations (50.3%) than among patients without symptoms-based exacerbations (37.3%; $P = .01$). Poor baseline sleep quality remained a significant risk factor for symptom-based exacerbations of COPD even after the researchers accounted for the effect of age, gender, body mass index, smoking, depression, angina, baseline inhaled respiratory medications, forced expiratory volume in 1 second %predicted, and modified Medical Research Council (mMRC) dyspnea scale (adjusted risk ratio, 1.09; 95% confidence interval, 1.01-1.18; $P = .02$).

Patients with at least one symptomatic exacerbation of COPD were significantly more likely to meet the threshold for poor sleep quality on the Pittsburgh Sleep Quality Index and have significantly higher median PSQI scores compared with patients without exacerbations (6.0 [interquartile range, 3.0 to 8.0] vs. 5.0 [2.0 to 7.0]; $P = .01$). Poor baseline sleep quality also was associated with event-based exacerbations and with a shorter time to symptoms-based exacerbations. Sleep disturbances, such as rising to void or experiencing respiratory issues or pain during sleep, correlated most strongly with symptoms-based exacerbations.

Sleep disruption can impede immune function and increase systemic inflammation, which might worsen COPD control and increase exacerbation risk The researchers acknowledged limitations to their study design. "Individuals with asthma or other obstructive lung diseases could not be definitively excluded; methacholine challenges were not performed. However, analyses excluding self-reported asthma were consistent with our main results. Second, because definitions of COPD exacerbation vary among studies, comparison may be limited,"

The CanCOLD study has received funding from the Canadian Respiratory Research Network, Astra Zeneca Canada, Boehringer Ingelheim Canada, GlaxoSmithKline Canada, Novartis, Merck Nycomed, Pfizer Canada, and Theratechnologies. Dr. Shorofsky had no disclosures. Several coinvestigators reported ties to GlaxoSmithKline, Novartis, Boehringer Ingelheim, Merck, Almirall, and Theratechnologies.

chestphysiciannews@chestnet.org

SOURCE: Shorofsky M et al. CHEST. 2019 May 28. doi: 10.1016/j.chest.2019.04.132.

FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.

POWER TO PREVENT EXACERBATIONS[1-3]

ACCORDING TO AN ANALYSIS OF NHANES DATA, 69% OF ADULT PATIENTS WITH ASTHMA HAD EOSINOPHILIC ASTHMA*[4]

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FASENRA is proven to reduce annual exacerbation rate in patients with severe eosinophilic asthma.[1-3]

NHANES=National Health and Nutrition Examination Survey.

*Data from the 2005 to 2006 annual survey of a nationally representative sample of a noninstitutionalized United States population in patients with asthma (aged 18-64 years) identified based on the participants' self-report. Eosinophilic asthma was defined as a blood eosinophil cutoff point of ≥150 cells/µL. Of the 310 adult patients, 69% had a blood eosinophil level ≥150 cells/µL.[4]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction.

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

CHARACTERISTICS OF PATIENTS WITH ALLERGIC OR NONALLERGIC EOSINOPHILIC ASTHMA[5,6]:

Elevated level of blood eosinophils

AND/OR

Frequent exacerbations (≥2 exacerbations annually)

ICS at high doses are insufficient to control the disease

CHOOSE FASENRA FOR PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA

IMPORTANT SAFETY INFORMATION (cont'd)

Parasitic (Helminth) Infection
It is unknown if FASENRA will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) include headache and pharyngitis.

Injection site reactions (eg, pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Please see additional Important Safety Information on next page and accompanying Brief Summary of full Prescribing Information.

Fasenra®
(benralizumab) Subcutaneous injection 30 mg
FROM THE START

FASENRA IS THE #1 RESPIRATORY BIOLOGIC

SELECTED BY PHYSICIANS FOR NEW PATIENTS IN SEVERE EOSINOPHILIC ASTHMA*[7]

*Data are not intended to suggest comparison of safety or efficacy to any other IL-5 or IL-5Rα treatment.[7]

STUDY DESIGNS

TRIALS 1 AND 2

Trial 1 (48-week) and Trial 2 (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing **FASENRA** 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (Trial 1) and 1306 (Trial 2) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (Trial 1) and medium- to high-dose ICS (Trial 2) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. Patients were stratified by geography, age, and blood eosinophil counts (≥300 cells/μL and <300 cells/μL). The primary endpoint was annual exacerbation rate ratio vs placebo in patients with blood eosinophil counts of ≥300 cells/μL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV_1 and total asthma symptom score at Week 48 (Trial 1) and Week 56 (Trial 2) in the same population.[2,3]

References: 1. FASENRA® (benralizumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017. **2.** Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115-2127. **3.** FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128-2141. **4.** Tran TN, Zeiger RS, Peters SP, et al. Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol*. 2016;116(1):37-42. **5.** de Groot JC, ten Brinke A, Bel EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res*. 2015;1:1-11. **6.** de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res*. 2016;2(2):1-8. **7.** Data on File, US-22015, AZPLP.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

INDICATION

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

- FASENRA is not indicated for treatment of other eosinophilic conditions
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus

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Fasenra® (benralizumab) Subcutaneous Injection 30 mg

FROM THE START

FASENRA® (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

Preparation and Administration

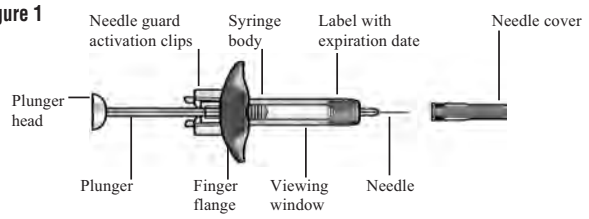
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Administer FASENRA within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

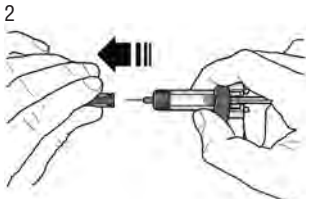
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

2



Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3

Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4

Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5

After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued *[see Contraindications (4) in the full Prescribing Information]*.

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

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

ADVERSE REACTIONS

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

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

Clinical Trials Experience

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

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14) in the full Prescribing Information]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n = 841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n = 822), and placebo (n = 847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1) in the full Prescribing Information]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N= 822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions**	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

** Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n = 73) or placebo (n = 75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14) in the full Prescribing Information]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see Data].

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

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

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n= 320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare professional if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

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Study IDs factors contributing to sleep clinic no-shows

BY DOUG BRUNK
MDedge News

SAN ANTONIO – Key determinants of no-show rates to a sleep clinic include being a new patient and lacking health insurance coverage, results from a single-center study showed.

"There are lots of people with sleep problems," one of the study's authors, Alvan Nzewuihe, MD, said in an interview at the annual meeting of the Associated Professional Sleep Societies. "However, we have to identify these patients to be able to help them. If they don't come to the sleep clinic [for assessment], we are going nowhere."

"Patients who are new to the clinic or have no insurance coverage have a higher odds of not showing up to their appointment and delaying their care."

In an effort to better understand determinants of no-show rates among sleep clinics, Dr. Nzewuihe and colleagues performed a 10-month, retrospective chart review of 2,532 patients scheduled at Saint Louis University's SLUCare Sleep Disorders Center during the months of July and October 2017 and April 2018. A no-show was determined if the patient failed to show up at their scheduled appointment on time or if they canceled their appointment. The researchers used multivariable logistic regression to determine which factors were independently associated with no-show rates.

Dr. Nzewuihe, a sleep medicine physician at the university, reported that the overall no-show rate during the study period was 21.2% and did not change with age, sex, or appointment factors such as time of day, day of week, or season of the year. Significant determinants of no-show rates included being a new patient (39.1% vs. 28.8% among established patients; *P* less than .0001) and having no health insurance (47.5% vs. public 28.3% vs private 24.2%; *P* less than .0001). Multivariate logistic regression confirmed the associations. New patients were 1.96 times more likely to not show up to the sleep clinic, compared with established patients, while patients with no health insurance coverage were 1.55 times more likely to not show up, compared with those with public health insurance.

Doug Brunk/MDedge News
Dr. Alvan Nzewuihe

The researchers wrote in their poster abstract, "Patients who are new to the clinic or have no insurance coverage have a higher odds of not showing up to their appointment and delaying their care. Efforts to prioritize high-risk patients of nonadherence will help contribute to better care and outcomes. Further studies are needed to develop methods to decrease no-show rates once high-risk appointments have been identified."

Dr. Nzewuihe acknowledged certain limitations of the study, including its retrospective design and the fact that other possible contributing factors were not evaluated such as literacy level, employment status, and length of time between appointment booking and appointment date. The study's first author was Julie Sahrmann, DO. The researchers reported having no financial disclosures.

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SOURCE: Sahrmann J et al. Sleep 2019, Abstract 0965.

Insomnia common among transgender college students

BY DOUG BRUNK
MDedge News

SAN ANTONIO – Compared with their cisgender counterparts, transgender college students are nearly three times more likely to be diagnosed with and treated for insomnia symptoms, results from a large national population-based survey showed.

"That was a stronger association than we expected," one of the study's researchers, Lisa B. Matlen, MD, said during an interview at the annual meeting of the Associated Professional Sleep Societies.

According to Dr. Matlen, a fellow in the division of sleep medicine at the University of Michigan, Ann Arbor, the transgender population is "extremely understudied" when it comes to research on sleep disturbances. In an effort to examine the prevalence of sleep disturbances and the association between transgender identity and sleep disturbances among transgender college students in the United States, she and her colleagues drew from the 2016 and 2017 American College Health Association National College Health Assessment II, a confidential, voluntary, electronically administered survey of college and university students. In all, 224,233 students were polled, and the researchers analyzed their responses to questions about gender identity, sleep symptoms, and diagnoses.

Doug Brunk/MDedge News
Dr. Lisa B. Matlen

The mean age of the respondents was 23 years, and most (82%) were undergraduate students. Of the 224,233 students, 3,471 (1.6%) self-identified as transgender. More than half of the transgender students (61.9%) were white, 10.6% were Hispanic/Latino, 10.5% were Asian or Pacific Islander, 6.3% were biracial or multiracial, 4.6% were black, and the rest were from other ethnicities. Compared with cisgender students, transgender students had increased odds of having sleep disturbances (odds ratio, 1.6), not feeling well rested on 4 or more days per week (OR, 1.8), going to bed early on 3 or more days per week due to sleepiness (OR, 1.3), and having insomnia 3 or more days per week (OR, 1.7). In addition, transgender students were nearly three times more likely to have an insomnia diagnosis and treatment, compared with their cisgender counterparts (OR, 2.9).

Transgender students were nearly three times more likely to have an insomnia diagnosis and treatment, compared with their cisgender counterparts.

Dr. Matlen acknowledged certain limitations of the study, including the fact that it drew from a population-based sample and that the survey was based on self-reported information. The study's first author was Ronald R. Gavidia Romero, MD. The researchers reported having no financial disclosures.

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SOURCE: Matlen LB et al. Sleep 2019.

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1 Goldhaber S, Visani L, DeRosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). The Lancet; Apr 24,1999; 353,9162; Health Module pg. 1386.

2 Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-486

3 Piazza, G., et al., "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." Journal of the American College of Cardiology: Cardiovascular Interventions.

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

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Lemborexant: Sex-based dosing not anticipated

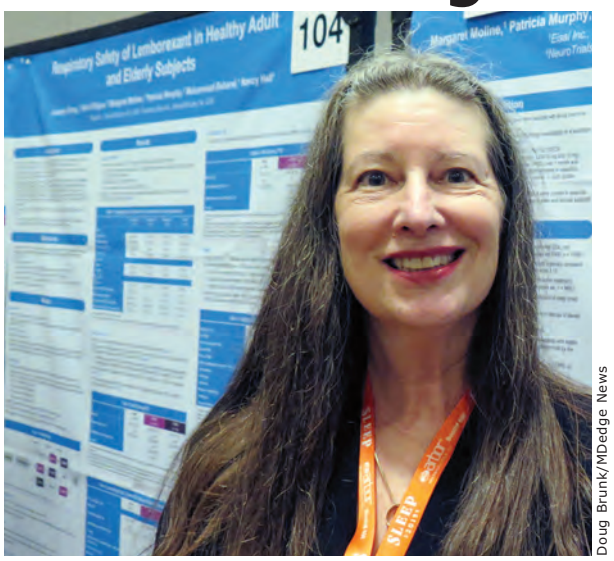
BY DOUG BRUNK
MDedge News

SAN ANTONIO – Lemborexant was effective in treating both sleep onset and maintenance variables in male and female subjects with insomnia, and it was well tolerated by both sexes, results from a pooled analysis showed.

A dual orexin receptor antagonist developed by Eisai, lemborexant is being studied as a treatment for insomnia disorder and irregular sleep-wake rhythm disorder. Early in 2019, the Food and Drug Administration accepted for review the New Drug Application for lemborexant for the treatment of insomnia. A target Prescription Drug User Fee Act date is set for Dec. 27, 2019.

"We evaluated early on whether exposure to lemborexant was going to be different between men and women," lead study author Margaret Moline, PhD, said during an interview at the annual meeting of the Associated Professional Sleep Societies. "With some drugs, like zolpidem and other so-called Z drugs, because exposure is different, clinical studies could involve different dosing for different sexes. Because we knew the exposure to lemborexant wasn't different between the sexes, we expected to see similar results in both sexes. That was the case."

Dr. Moline, executive director of the Neurology Business Group and International Project Team Lead for the lemborexant clinical development program at Eisai, and colleagues presented pooled analyses of subject-reported sleep-onset latency (sSOL) and subject-reported wake after sleep onset (sWASO) from lemborexant phase 3 studies, SUNRISE-1 and SUNRISE-2. SUNRISE-1 was a 1-month, double-blind, placebo- and active-controlled, parallel-group study in 1,006 subjects. Participants were females aged



Doug Brunk/MDedge News

Dr. Margaret Moline

55 years and older and males aged 65 years and older with a primary complaint of sleep maintenance difficulties and an Insomnia Severity Index (ISI) total score of 13 or higher. SUNRISE-2 was a placebo-controlled, 6-month, active treatment, double-blind, parallel-group study in 949 subjects with insomnia disorder. Participants were females and males aged 18 years and older with a primary complaint of sleep onset and/or sleep maintenance difficulties and an ISI total score of 15 or higher. Both analyses included subjects randomized to placebo, lemborexant 5 mg, or lemborexant 10 mg. Each study included a single-blind placebo run-in period prior to randomization.

The pooled analysis of 1,693 subjects included 402 (23.7%) men and 1,291 (76.3%) women. Results on sSOL and sWASO were consistent with the significant results on sleep diary in the individual studies. In both sexes, sSOL for lemborexant 5 mg and lemborexant 10 mg was significantly reduced versus that for placebo during the first 7 days and end of month 1 (P less than .05 for all comparisons). In women, the researchers observed significantly greater reductions in sWASO placebo for both lemborexant doses versus that with placebo (first 7 days and end of month 1; P less than .0001 for all comparisons). In males, sWASO decreased significantly, compared with placebo, for the first 7 days (lemborexant 5 mg and lemborexant 10 mg; P equal to or less than .0001) and at end of month 1 (lemborexant 10 mg only; $P = .0032$). For placebo, lemborexant 5 mg, and lemborexant 10 mg, the overall incidence of treatment-emergent adverse events was similar across sexes. Incidence of treatment-emergent serious adverse events was low for both sex subgroups; most events occurred in one subject each. Treatment-emergent adverse events leading to study drug withdrawal or interruption were few and similar across sexes for all treatments and was highest in males receiving lemborexant 10 mg. The most frequent treatment-emergent adverse events reported in males were somnolence, fatigue, and headache, while the most common in females were somnolence, headache, and urinary tract infection. About 3% of females (no males) reported a urinary tract infection; the incidence in females was similar across treatment groups.

"Overall, sleep diary outcomes in males and females were consistent with the significant results observed in the total populations of the individual studies," Dr. Moline concluded. "A dose adjustment based on sex is not anticipated."

The research was supported by Eisai. Dr. Moline is an employee of the company.

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SOURCE: Moline M et al. Sleep 2019, Abstract 0368.

CPAP for infants with OSA is effective, with high adherence

BY TARA HAELLE
MDedge News

DALLAS – Continuous positive airway pressure (CPAP) is an effective, feasible treatment for infants with obstructive sleep apnea (OSA), according to a study.

"Positive airway pressure is a common treatment for OSA in children," wrote Christopher Cielo, DO, of Children's Hospital of Philadelphia Sleep Center, and his colleagues. But the authors note that treating infants with CPAP can be more challenging because infants have less consolidated sleep, may have greater medical complexity, and have smaller faces that make mask fit, titration, and adherence difficult.

The researchers therefore compared use of CPAP for OSA on 32 infants who began the therapy before age 6 months and 102 school-age children who began the therapy between ages 5 and 10 years, all treated at a single sleep center between March 2013 and September 2018.

Only one of the infants (mean age 3 months) had obesity, compared with 37.3% of the school-age children (mean age 7.7 years), but more of the infants (50%) had a craniofacial abnormality compared with the older children (8.9%) (P less than .001).

None of the infants had had an adenotonsillectomy, whereas the majority of the older children (80.4%) had (P less than .001). Rates of neurological abnormality and genetic syndromes (including Down syndrome) were similar between the groups.

In baseline polysomnograms, infants had a higher mean obstructive apnea-hypopnea index (AHI) compared with older children (22.6 vs. 12; P less than .001) and a slightly, but significantly, lower oxygen saturation nadir (81% vs. 87%; $P = .002$).

Only 9.8% of the children and none of the infants used autotitrating. Similar proportions of both groups – 90.6% of infants and 93.1% of children – achieved a mean AHI below 5 with CPAP treatment, and both CPAP pressure and mean oxygen saturation nadir at final pressure were similar in both groups.

Adherence was higher in infants than in children: Infants used CPAP for at least some time for 93.3% of nights compared with children (83.4%) ($P = .009$), and infants used CPAP for more than 4 hours for 78.4% of nights, compared with 59.5% of nights among children ($P = .04$).

Barriers to adherence reported by caregivers were similar between both groups. The most common barrier was child behavior, such as crying or refusing the CPAP, which 25% of infant caregivers and 35.3% of child caregivers reported. While a higher proportion of caregivers reported a poor mask fit for infants (15.6%) than for children (10.8%), the difference was not significant ($P = .47$). Rates of skin irritation also did not significantly differ between the groups.

In addition to the limitations accompanying any retrospective analysis from a single center, another study limitation was the inability to account for differences in total sleep time between infants and school-age children in comparing CPAP usage.

The National Institutes of Health and the Francis Family Foundation funded the research. The authors had no disclosures.

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SOURCE: Cielo C et al. ATS 2019, Abstract A2786.

Briefest flash of light can alter the circadian system

BY DOUG BRUNK
MDedge News

SAN ANTONIO – The human circadian system can be phase shifted by flashes of dim light that last as little as 10 microseconds, results from a novel study showed.

"This becomes a complementary way to help people with various kinds of circadian phase disorders," the study's first author, Jamie M. Zeitzer, PhD, said during an interview at the annual meeting of the Associated Professional Sleep Societies. "Right now under ideal laboratory circumstances, you can change someone's circadian timing by about 3 hours. That's not happening in the real world; that's what you do in a lab. That's with very bright light for 6 hours and very dim light the rest of the time."

In an effort to build on previous literature related to circadian phase shifting and continuous light exposure in rodents and in humans, Dr. Zeitzer, of the department of psychiatry and behavioral sciences at Stanford (Calif.) University, and colleagues enrolled 56 healthy young men and women in their 20s and 30s to take part in two parallel 16-day studies. For the first 14 days, study participants maintained a regular sleep/wake cycle at home as confirmed through actigraphy and sleep logs. They spent the final 2 days in a specialized time-isolation laboratory, during which the phase of the circadian pacemaker (salivary melatonin onset) was determined in constant routine conditions on

Doug Brunk/MDedge News

Dr. Jamie M. Zeitzer

evening one and two; light exposure occurred between these two phase determinations on night one.

Light exposure consisted of 1 hour of a sequence of light flashes delivered through a pair of modified welding goggles during enforced wake starting 2 hours after habitual bedtime. Flashes were presented every 15 seconds and varied either by duration (from 10 microseconds to 10 seconds at a fixed intensity of 2,200 lux) or intensity (a range between 3 and 9,500 lux, with a duration fixed at 2 milliseconds).

Dr. Zeitzer and colleagues observed no significant difference in the phase shift created between flashes that were given at 10 microseconds and flashes that were given at 10 seconds. "That's a six-log unit variation," he said during a presentation of the results at the meeting. "There are a million times more photons given in 10-second flashes over the hour than there are in the 10-microsecond flashes. Despite the fact that there are a million more photons, you get the exact same phase shift in both of these conditions. You need very little light in order to generate these phase shifts. You're talking about less than 1 second of light stretched out over 1 hour."

The researchers also observed that flash intensity showed a sigmoidal relationship with phase shifting, with a half-maximal shift observed at 8 lux and 90% of the maximal shift occurring after exposure to flashes as dim as 50 lux. None of the flash sequences caused acute suppression of melatonin.

"We did not anticipate the invariance, that anything from 10 microseconds to 10 seconds gives us no difference [in phase shifting]," Dr. Zeitzer said. "That was surprising. I thought that more light would be slightly less effective in terms of photons but still give a bigger [phase] shift, but that didn't happen. In the intensity response, we see things are more sensitive to light flashes than they are to continuous light, which is also surprising. It implies that a different part of the eye is responding to light flashes than it is to continuous light. It provides more information about how to minimize the amount of light we're using and maximize the amount of shift."

Which photoreceptors underlie the responses remains unclear, he continued, "but given the characteristics of photoreceptors, our hypothesis is that flashes are being mediated through a cone cell response, while the response to continuous light is being primarily mediated through a melanopsin response. A future question we plan to investigate is, can selective sequential simultaneous activation of different photoreceptors create enhanced phase shifts?"

The study was supported by the Department of Defense. Dr. Zeitzer reported having no financial disclosures.

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SOURCE: Zeitzer JM et al. SLEEP 2019.

Sleep quality linked to gut microbiome biodiversity

BY DOUG BRUNK
MDedge News

SAN ANTONIO – Better sleep quality and less sleepiness, but not sleep duration, are significantly associated with greater species richness and diversity of the gut microbiota, according to results from a population sample of adults.

"These findings are preliminary and very early in the growth of this field," lead study author Erika W. Hagen, PhD, said during an interview at the annual meeting of the Associated Professional Sleep Societies

According to Dr. Hagen, an epidemiologist at the University of Wisconsin–Madison, experimental studies in mice have shown that disturbed sleep is associated with gut microbiota composition, and a few small experimental studies in humans have found associations between curtailed sleep and measures of gut microbiota richness and diversity.

In an effort to examine associations of subjectively and objectively assessed sleep metrics with indices of gut microbiome richness and diversity, Dr. Hagen and colleagues assessed 482 individuals who participated in the Survey of the Health of Wisconsin and completed in-home study visits in 2016. They provided fecal samples, participated in a week-long wrist actigraphy protocol to measure sleep, and completed questionnaires about sleep, diet, and other health and sociodemographic factors, and an assessment of physical activity by waist-worn actigraphy.

Metrics of species richness included the Chao1 and the ACE, which estimate the number of species. Metrics of the diversity of the gut microbiome included the Inverse Simpson index and the Shannon index. All metrics were regressed on self-reported sleep duration, extreme daytime sleepiness, the Epworth Sleepiness Scale (ESS), and actigraphy-measured sleep duration and wake after sleep onset (WASO). Next, the researchers estimated associations between each of the sleep and diversity measures separately, adjusting for age and sex and then additionally adjusting for body mass index, moderate-vigorous physical activity, and dietary fat and fiber.

The mean age of the 482 subjects was 56 years, 57% were female, and the mean body mass index was 30 kg/m^2. After the researchers adjusted for gender and age, they found that greater WASO was statistically significantly associated with lower richness and alpha diversity (P less than .05). These associations remained significant on the Chao1 measure and borderline significant on the ACE and Shannon measures after further adjustment for BMI, physical activity, and dietary fiber and fat. For example, 60 minutes greater WASO was associated with an approximate 26% population standard deviation reduction in microbial richness as measured by Chao1. In fully-adjusted models, greater daytime sleepiness was associated with lower richness and diversity on all indices (P = .01-.06).

"Our results suggest that sleep quality is associated with gut microbiome richness and diversity," Dr. Hagen said. "Our results are in line with other research on this topic. What's interesting is how your sleep over a period of time is affecting these measures of your microbiome. That's something people can do something about with [eating] habits over time."

She acknowledged certain limitations of the study, including the small sample size and the cross-sectional design. The study was supported by the University of Wisconsin School of Medicine and Public Health through the Wisconsin Partnership Program.

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SOURCE: Hagen EW et al. SLEEP 2019, Abstract 0106.

Lung disease + screen time impact sleep quality

BY TARA HAELLE
MDedge News

DALLAS – Children with cystic fibrosis or asthma report sleep interruptions 1 or 2 nights a week caused by their symptoms, but nighttime use of technology may contribute more to sleep problems, according to a new study.

"Routinely addressing sleep concerns, sleep hygiene, and mental health is important in the care of pediatric patients with chronic illness," concluded Lauren Greenawald, DO, and colleagues at the Alfred I. duPont Hospital for Children in Wilmington, Del. The researchers presented their findings on sleep quality and mental health of children with asthma or cystic fibrosis (CF) at the American Thoracic Society's international conference.

Dr. Greenawald's team screened 31 children (aged 7-17 years) with CF and 34 children with asthma for anxiety, depression, and ADHD. The researchers also assessed the children's sleep hygiene, sleep quality, and physical and emotional symptoms. Instruments included the validated Pediatric Daytime Sleepiness Scale (PDSS), Pediatric Quality of Life Inventory, and Patient-Reported Outcomes Measurement Information System Pediatric Anxiety Survey, plus an investigator-designed survey about sleep habits.

Just over half the children with CF (52%) and 14% of children with asthma had mental health diagnoses (*P* less than .01). The same proportion of patients with CF (52%) and nearly a third of patients with asthma (30%) reported they often or always felt they needed more sleep based on the PDSS.

Further, 42% of children with CF and 55% of children with asthma said their symptoms kept them awake 1-2 nights a week. Only 6% of asthma patients and no CF patients said their symptoms keep them awake often, 3-4 nights a week. Just over a third of children with CF (36%) and 46% of those with asthma thought they would sleep better if they didn't have a medical condition.

Yet, for the vast majority of children, the sleeping problems did not appear to result from worry about their illness: 85% of those with CF and nearly all of those with asthma (97%) did not have trouble sleeping as a result of anxiety about their medical condition.

The researchers identified nighttime use of technology that may affect the children's sleep in ways similar to that of the general population. Many of the participants – 68% of those with CF and 47% of those with asthma – reported texting or using social media or other technology an hour before going to bed. In addition, 55% of those with CF and 25% of those with asthma said they use their phone after the lights are out at least 5 nights a week. One in five of those with CF (20%) said they go to bed later than they planned at least 5 days a week because of social media or texting, though only 6% of those with asthma said the same.

Despite the children's reports of inadequate sleep, very few – 3.2% of children with CF and 5.9% of children with asthma – reported feeling low daytime energy.

The use of child self-reporting in the presence of family members is a study limitation, including potentially introducing social desirability bias.

The research was funded by the Nemours Summer Undergraduate Research Program. The authors reported no disclosures.

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SOURCE: Greenawald L et al. ATS 2019, Abstract A2788.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Every day, parents are giving their BABIES cell phones in my exam room to "entertain" or "pacify" them with videos or Youtube. And when I talk to adolescents about no screen time 1 hour prior to bedtime, they comment "it's okay because I have it on the dimmer light at night." This report is extremely important!

CF drug picks up indication for children as young as 6

BY M. ALEXANDER OTTO
MDedge News

The Food and Drug Administration has expanded the indication for an oral tezacaftor/ivacaftor combination for cystic fibrosis (Symdeko), to include children as young as 6 years old.

The drug was approved in 2018 for patients aged 12 years and older who have the most common cause of the disease, two alleles for the F508del mutation in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, or at least one other CFTR mutation responsive to the combination, as listed in labeling.

The original approval was based on three phase 3, double-blind, placebo-controlled trials, which demonstrated improvements in lung function and other key measures of the disease. One trial that found a 6.8% mean improvement in lung function testing over placebo at 8 weeks, and another that found a 4% improvement at 24 weeks, with fewer respiratory exacerbations and improved respiratory-related quality of life. A third trial in patients without the indicated genetic mutations was ended early for futility.

The efficacy in children under 12 years was extrapolated from those trials, plus an open-label study that found similar effects.

Labeling warns of elevated liver enzymes and cataracts in children, and notes that the drug should be taken with food that contains fat. Labeling also recommends against use with strong cytochrome P450 3A4 (CYP3A) inducers – rifampin, phenobarbital, St. John's wort, among others – because they might reduce efficacy, and against use with CYP3A inhibitors – ketoconazole, clarithromycin, Seville oranges, grapefruit juice, etc. – because of the risk of increased exposure.

The most common side effects are headache, nausea, sinus congestion, and dizziness. The FDA has cleared a CF gene test to check for the required mutations. Symdeko is marketed by Vertex Pharmaceuticals.

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Penicillin-susceptible *Streptococcus pneumoniae* most common cause of bacteremic CAP

BY JILL D. PIVOVAROV
MDedge News

A study found that only 2% of children hospitalized with community-acquired pneumonia (CAP) actually had any causative pathogen in their blood culture results, despite national guidelines that recommend blood cultures for all children hospitalized with moderate to severe CAP.

The guidelines are the 2011 guidelines for managing CAP published by the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) (Clin Infect Dis. 2011 Oct;53[7]:617-30).

Cristin O. Fritz, MD, of the Children's Hospital of Colorado, Aurora, and associates conducted a data analysis of the EPIC (Etiology of Pneumonia in the Community) study to estimate prevalence, risk factors, and clinical outcomes in children hospitalized with bacteremic CAP and to evaluate the relationship between positive blood culture results, empirical antibiotics, and changes in antibiotic treatment regimens.

Data were collected at two Tennessee hospitals and one Utah hospital during Jan. 1, 2010–June 30, 2012. Of the 2,358 children with CAP enrolled in the study, 2,143 (91%) with blood cultures were included in Dr. Fritz's analysis. Of the 53 patients presenting with positive blood culture results, 46 (2%; 95% confidence interval: 1.6%-2.9%) were identified as having bacteremia. Half of all cases observed were caused by *Streptococcus pneumoniae*, with *Staphylococcus aureus* and *Streptococcus pyogenes* noted less frequently, according to the study published in Pediatrics.

A previous meta-analysis of smaller studies also found that children with CAP rarely had positive blood culture results, a pooled prevalence of 5% (Pediatr Infect Dis J. 2013;32[7]:736-40). Although it is believed that positive blood culture results are key to narrowing the choice of antibiotic and predicting treatment outcomes, the literature – to date – reveals a paucity of data supporting this assumption.

Overall, children in the study presenting with bacteremia experienced more severe clinical outcomes, including longer length of stay, greater likelihood of ICU admission, and invasive mechanical ventilation and/or shock. The authors also observed that bacteremia was less likely to be detected in children given antibiotics after admission but before cultures were obtained (0.8% vs 3%; $P = .021$). Pleural effusion detected with chest radiograph also consistently indicated bacteremic pneumonia, an observation made within this and other similar studies.

Also of note in detection is the biomarker procalcitonin, which is typically present with bacterial disease. Dr. Fritz and colleagues stressed that, because the procalcitonin rate was higher in patients presenting with bacteremia, "this information could influence decisions around culturing if results are rapidly available."

Compared with other studies reporting prevalence ranges of 1%-7%, the prevalence of bacteremia in this study is lower at 2%. The authors attributed the difference to a possible potential limitation with the other studies, for which culture data were only available for a median 47% of enrollees. Dr. Fritz and her colleagues caution that, "because cultures were obtained at the discretion of the treating clinician in a majority of studies, blood cultures were likely obtained more often in those with more severe illness or who had not already received antibiotics."

The authors observed that penicillin-susceptible *S. pneumonia* was the most common cause of bacteremic CAP. They further acknowledged that their study and findings by Neuman et al. in 2017 give credence to the joint 2011 PIDS/IDSA guideline recommending narrow-spectrum aminopenicillins specifically to treat children hospitalized due to suspected bacterial CAP.

Despite its small sample size, the results of this study clearly demonstrate that children with bacteremia because of *S. pyogenes* or *S. aureus* experience increased morbidity, compared with children with *S. pneumoniae*, they said

While this is acknowledged to be one of the largest studies of its kind to date, a key limitation was the small number of observable patients with bacteremia, which prevented the researchers from conducting a more in-depth analysis of risk factors and pathogen-specific differences. That one-fourth of patients received inpatient antibiotics before cultures could be collected also likely led to an underestimation of risk factors and misclassification bias.

"In an era with widespread pneumococcal vaccination and low prevalence of bacteremia in the United States, children admitted with CAP that have pleural effusion or require ICU admissionmay represent a high-yield population for identifying bacteremia," they wrote.

Dr. Fritz had no conflicts of interest to report. Some coauthors cited multiple sources of potential conflict of interest related to consulting fees, grant support, and research support from various pharmaceutical companies and agencies. The study was funded by the National Institutes of Health and in part by a grant from the National Institute of Allergy and Infectious Diseases.

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SOURCE: Fritz CO et al. Pediatrics. 2019;144(1):e20183090.

10-valent pneumococcal vaccine effective in boys and girls

BY LUCAS FRANKI
MDedge News

A 10-valent pneumococcal conjugate vaccine appeared equally effective against pneumococcal disease in boys and girls, according to Heta Nieminen, MD, of the National Institute for Health and Welfare in Tampere, Finland, and associates.

For the study, published in Vaccine, the investigators conducted a post hoc analysis of the phase 3/4, cluster-randomized, double-blind FinIP trial, in which more than 30,000 infants received the PHiD-CV10 vaccine or a placebo. Patients were aged less than 7 months when they received their first vaccination, and received two or three primary doses, plus a booster shot after the age of 11 months.

In term infants, vaccine effectiveness was similar in boys and girls; while the vaccine worked marginally better in girls, the difference was not significant. Infants who received the 2 + 1 schedule had vaccine effectiveness similar to that of those who received the 3 + 1 schedule. In a smaller subanalysis of 1,519 preterm infants, outcomes of pneumonia were more common, but the vaccine seemed to confer protection, although the sample size was not large enough for statistical significance to be reached.


MarianVejcik/Getty Images

"The point estimates of vaccine effectiveness suggest protection in both sexes, and also among the preterm and low-birth-weight infants. ... There were no significant differences between the 2 + 1 and 3 + 1 schedules in any of the subgroups analyzed. Based on this study, the 2 + 1 or "Nordic" schedule is sufficient also for the risk groups such as the preterm or low-birth-weight infants," the investigators concluded.

Five study authors are employees of the National Institute for Health and Welfare, which received funding for the study from GlaxoSmithKline. Four coauthors are employees of GlaxoSmithKline; three of them own shares in the company.

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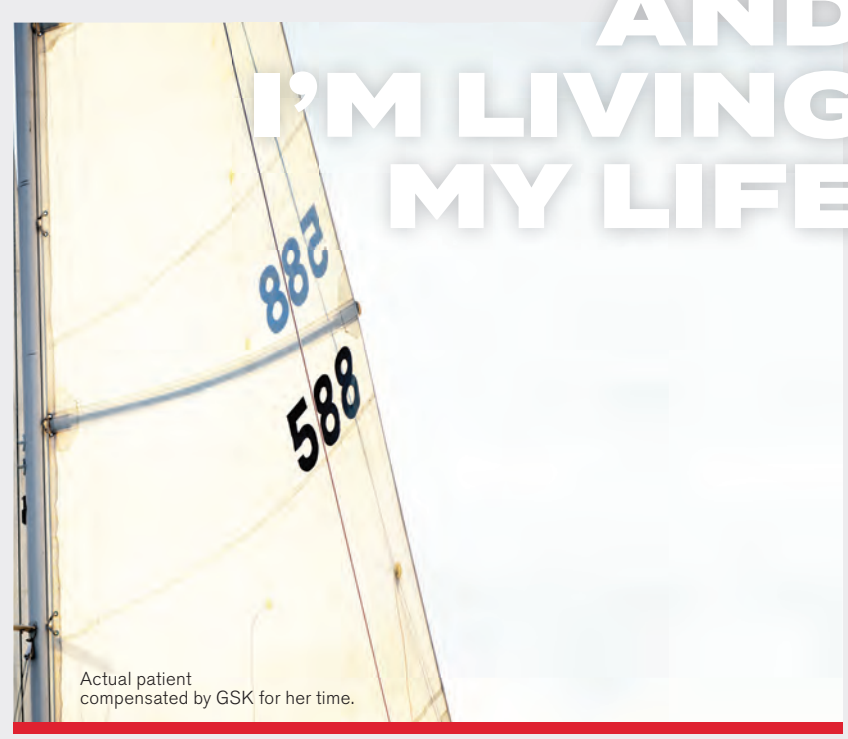
SOURCE: Nieminen H et al. Vaccine. 2019 May 20. doi: 10.1016/j.vaccine.2019.05.033.

NUCALA is indicated for the add-on maintenance treatment of patients 12 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 5/19 (All rights reserved).

†December 2015 to May 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

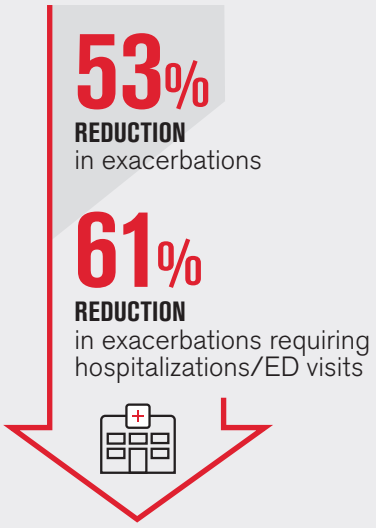
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms 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[1]

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 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 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[1]: 4.5-year open-label study assessing the safety, immunogenicity, and efficacy of NUCALA 100 mg added to asthma controller therapy in 347 patients 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.

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

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Nucala
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

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 12 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

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). 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 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 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.

6.3 Immunogenicity

In subjects with asthma receiving NUCALA 100 mg, 15/260 (6%) developed 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.

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 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.

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8 USE IN SPECIFIC POPULATIONS (cont'd)

8.4 Pediatric Use
The safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the Phase 3 asthma studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) 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 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 NUCALA 100 mg and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.
The safety and efficacy in pediatric patients other than those with 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 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.
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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Cardiovascular burden driven by unmet social needs

BY JENNIFER REISING
MDedge News

WASHINGTON – Having unmet social needs plays a key role in raising the risk of cardiovascular disease among immigrant, socially isolated, and low-income populations, according to a study.

"Although there have been great medical interventions and our technology keeps improving, we can't prevent the burden of cardiovascular disease. It's the social factors that are playing this role," said Ana Palacio, MD, MPH, of the University of Miami during her presentation of the study findings at the annual meeting of the Society of General Internal Medicine.

"The most surprising finding was how much weight the social factors have in adding to the Framingham risk score, in taking a patient from a medium score to a higher score because of their social environment."

"We need to address issues at the patient's home, such as food, isolation, and transportation, to help them prevent cardiovascular risk," she added.

The study was designed to determine how patient-reported social determinants of health (SDH) had an effect on the Framingham risk score (FRS). Researchers also wanted to assess the relationship between the SDH score and individual risk factors for cardiovascular health, including blood pressure, hemoglobin A_{1c}, LDL cholesterol, body mass index, tobacco use, and physical activity.

Results showed that several SDH factors significantly increase the FRS score, including being born outside of the United States, living alone, having a high social isolation score, and having a low geocoded-based median household income (*P* less than .01). The calculated SDH score ranged from 0 to 59.

Higher SDH scores were associated with high FRS scores in the areas of poor blood pressure and diabetes control. Additionally, those who had financial strain, poor health literacy, stress, lack of education, and a low median household income were more likely to have a sedentary lifestyle. Black or Hispanic patients who were born outside the United States and had low median household income were at a higher risk of obesity.

The study also shows the prediction of poor blood pressure and diabetes control was superior through the 11,153 SDH self-survey responders, compared with census data. In the self-reported SDH survey, the predicted blood pressure was 0.74 (0.71-0.76) and the diabetes predictor was 0.77 (0.75-0.80). While the census-based deprivation index predicted blood pressure was 0.68 (0.64-0.70) and diabetes control was 0.73 (0.71-0.76). The retrospective cohort study originally involved 11,113 primary care patients who received care at the University of Miami Health System between Sept. 16, 2016, and Sept. 10, 2017, and answered an SDH survey. Of this group, 2,876 patients completed the electronic health record data to compile a score. This population had a mean age of 53.8 years and was 61% female; 38% were Hispanic and 9% were black. The mean household income was $53,677 and 87% reported speaking English.

The study examined a total of 11 self-reported and census-based SDH factors. The self-reported factors were race/ethnicity, education, financial strain, stress, tobacco use and physical activity, social isolation, years living in the United States, health literacy, and delayed care. The remaining factors were based on an area deprivation index and census-driven median household income.

"The most surprising finding was how much weight the social factors have in adding to the Framingham risk score, in taking a patient from a medium score to a higher score because of their social environment," said Dr. Palacio.

The study was funded by the Precision Medicine and Health Disparities Collaborative and was supported by the National Institute on Minority Health and Health Disparities and National Human Genome Research Institute of the National Institutes of Health.

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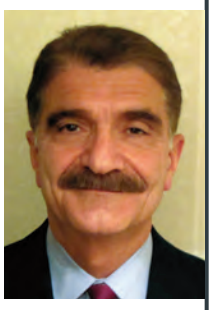
VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: This is a timely report adding science behind the well-known impact of poverty and lack of social resources on the well-being of the underserved minorities. It is in line with a published report from the University of Virginia group on the impact of these social factors on surgical outcomes after cardiac surgery (Ann Thorac Surg. Jun 2019;107:1706-12). The challenge for physicians is how to optimize the care of these patients to improve their outlook.

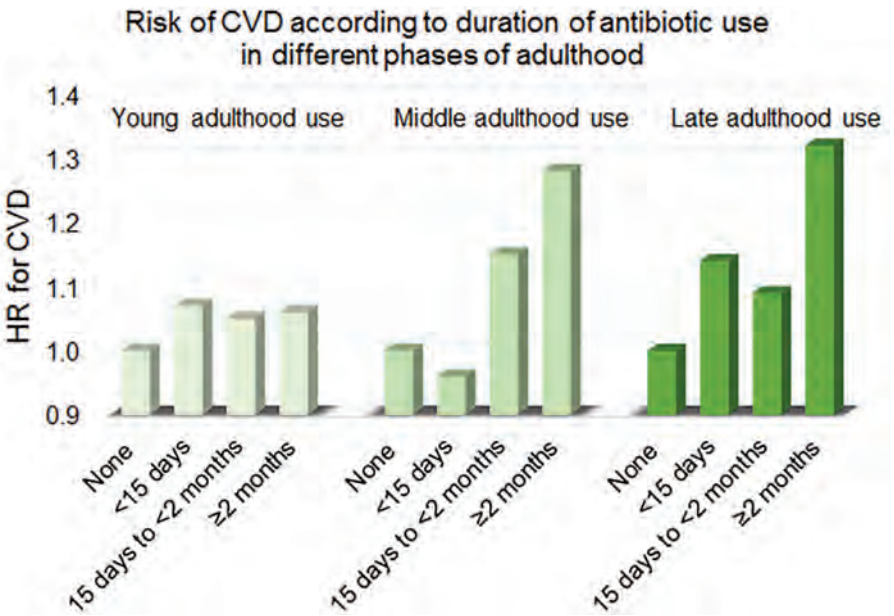
Long-term antibiotic use may heighten stroke, CHD risk

BY JAKE REMALY
MDedge News

Among middle-aged and older women, 2 or more months' exposure to antibiotics is associated with an increased risk of coronary heart disease or stroke, according to a study in the European Heart Journal.

Women in the Nurses' Health Study who used antibiotics for 2 or more months between ages 40 and 59 years or at age 60 years and older had a significantly increased risk of cardiovascular disease, compared with those who did not use antibiotics. Antibiotic use between 20 and 39 years old was not significantly related to cardiovascular disease.

Prior research has found that antibiotics may have long-lasting effects on gut microbiota and relate to cardiovascular disease risk.



European Heart Journal and Professor Lu Qi, Tulane

"Antibiotic use is the most critical factor in altering the balance of microorganisms in the gut," said lead investigator Lu Qi, MD, PhD, in a news release. "Previous studies have shown a link between alterations in the microbiotic environment of the gut and inflammation and narrowing of the blood vessels, stroke, and heart disease," said Dr. Qi, who is the director of the Tulane University Obesity Research Center in New Orleans and an adjunct professor of nutrition at Harvard T.C. Chan School of Public Health in Boston.

To evaluate associations between life stage, antibiotic exposure, and subsequent cardiovascular disease, researchers analyzed data from 36,429 participants in the Nurses' Health Study. The women were at least 60 years old and had no history of cardiovascular disease or cancer when they completed a 2004 questionnaire about antibiotic usage during young, middle, and late adulthood. The questionnaire asked participants to indicate the total time using antibiotics with eight categories ranging from none to 5 or more years.

The researchers defined incident

Continued on following page

Continued from previous page

cardiovascular disease as a composite endpoint of coronary heart disease (nonfatal myocardial infarction or fatal coronary heart disease) and stroke (nonfatal or fatal). They calculated person-years of follow-up from the questionnaire return date until date of cardiovascular disease diagnosis, death, or end of follow-up in 2012.

Women with longer duration of antibiotic use were more likely to use other medications and have unfavorable cardiovascular risk profiles, including family history of myocardial infarction and higher body mass index. Antibiotics most often were used to treat respiratory infections. During an average follow-up of 7.6 years, 1,056 participants developed cardiovascular disease.

In a multivariable model that adjusted for demographics, diet, lifestyle, reason for antibiotic use, medications, overweight status, and other factors, long-term antibiotic use – 2 months or more – in late adulthood was associated with significantly increased risk of cardiovascular disease (hazard ratio, 1.32), as was long-term antibiotic use in middle adulthood (HR, 1.28).

Although antibiotic use was self-reported, which could lead to misclassification, the participants were health professionals, which may mitigate this limitation, the authors noted. Whether these findings apply to men and other populations requires further study, they said. Because of the study's observational design, the results "cannot show that antibiotics cause heart disease and stroke, only that there is a link between them," Dr. Qi said. "It's possible that women who reported more antibiotic use might be sicker in other ways that we were unable to measure, or there may be other factors that could affect the results that we have not been able take account of."

"Our study suggests that antibiotics should be used only when they are absolutely needed," he concluded. "Considering the potentially cumulative adverse effects, the shorter time of antibiotic use the better."

The study was supported by National Institutes of Health grants, the Boston Obesity Nutrition Research Center, and the United States–Israel Binational Science Foundation. One author received support from the Japan Society for the Promotion of Science. The authors had no conflicts of interest.

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SOURCE: Heianza Y et al. Eur Heart J. 2019 Apr 24. doi: 10.1093/eurheartj/ehz231.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: This large observational study provides evidence for a link between long-term use of antibiotics and the increased risk of cardiovascular disease in older women. This challenges the physicians in being more selective in their prescription of antibiotics for their patients. In support of the authors' suggestion on the potential role of gut microbiome on dietary metabolites, some recent publications on this topic are worth reading (Eur Heart J. 2019 Apr 23; https://doi.org/10.1093/eurheartj/ehz259; JAMA. 2019;321[22]:2149-51; J Am Heart Assoc. 2017;6[7]:e004947).

Dexmedetomidine fails to reduce 90-day mortality in ICU patients supported by mechanical ventilation

BY JEFF CRAVEN
MDedge News

Dexmedetomidine fell short for reducing 90-day mortality as the primary sedative for patients on mechanical ventilation, according to results of the randomized, controlled, open-label SPICE III trial, which was presented at the annual meeting of the American Thoracic Society and simultaneously published in the New England Journal of Medicine.

"Among patients undergoing mechanical ventilation in the ICU, those who received early dexmedetomidine for sedation had a rate of death at 90 days similar to that in the usual-care group and required supplemental sedatives to achieve the prescribed level of sedation," Yahya Shehabi, PhD, of Monash University in Clayton, Australia, and colleagues wrote.

The study was conducted in 74 ICUs in eight countries. Researchers randomly assigned 4,000 patients who were critically ill, had received ventilation for less than 12 hours, and were likely to require mechanical ventilation for at least the next day to either dexmedetomidine or usual care (propofol, midazolam, or another sedative).

The sedation goal was a Richmond Agitation and Sedation Scale (RASS) score of –2 (lightly sedated) to +1 (restless), and was assessed every 4 hours. Intravenous dexmedetomidine was administered at 1 mcg/kg of body weight per hour without a loading dose and adjusted to a maximum dose of 1.5 mcg/kg per hour to achieve a RASS score in the target range. Use was continued as clinically required for up to 28 days.

The modified intention-to-treat analysis included 3,904 patients. The 90-day mortality rate was 29.1% (556 of 1,948 patients) for patients who received dexmedetomidine and 29.1% (569 of 1,956 patients) for those who received usual care. There was no significant difference for patients with suspected or proven sepsis at randomization and those without sepsis. Mortality did not vary based on country, cause of death, or discharge destination.

Dr. Shehabi and colleagues noted that, for 2 days after randomization, patients who received dexmedetomidine were also given propofol (64% of patients), midazolam (3%), or both (7%) as supplemental sedation. In the control group, 60% of the patients received propofol, 12% received midazolam, and 20% received both. About 80% of patients in both groups received fentanyl. The use of multiple agents may reflect sedation requirements during the acute phase of critical illness.

With regard to adverse events, the patients receiving dexmedetomidine more commonly experienced bradycardia and hypotension than the usual-care group.

SPICE III was funded in part by a grant from the National Health and Medical Research Council of Australia and the National Heart Institute of Malaysia. Dr. Shehabi reports grants from the National Health and Medical Research Council of Australia, nonfinancial and other support from Pfizer, and nonfinancial and other support from Orion Pharma.

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SOURCE: Shehabi Y et al. N Engl J Med. 2019 May 19. doi: 10.1056/NEJMoa1904710.

Elevated monocyte count predicted poor outcomes in idiopathic pulmonary fibrosis

BY JAKE REMALY
MDedge News

An increased monocyte count at the time of diagnosis predicts poor outcomes among patients with idiopathic pulmonary fibrosis and other fibrotic diseases, including hypertrophic cardiomyopathy, systemic sclerosis, and myelofibrosis, according to research published in The Lancet Respiratory Medicine.

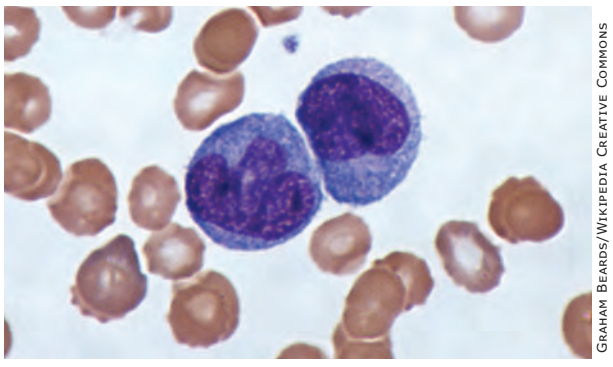
The data indicate that "a single threshold value of absolute monocyte counts of 0.95 K/mcL could be used to identify high-risk patients with a fibrotic disease," said Madeleine K.D. Scott, a researcher at Stanford (Calif.) University, and coauthors.

While other published biomarkers – including gene panels and multicytokine signatures – may be expensive and not readily available, "absolute monocyte count is routinely measured as part of a complete blood count, an inexpensive test used in clinical practice worldwide," the authors said.

A retrospective multicenter cohort study

To assess whether immune cells may identify patients with idiopathic pulmonary fibrosis at greater risk of poor outcomes, Ms. Scott and her collaborators conducted a retrospective multicenter cohort study.

They first analyzed transcriptome data from 120 peripheral blood mononuclear cell samples of patients with idiopathic pulmonary fibrosis, which they obtained from the Gene Expression Omnibus at the National Center for Biotechnology Information. They used statistical deconvolution to



Graham Beards/Wikipedia Creative Commons

estimate percentages of 13 immune cell types and examined their associations with transplant-free survival. Their discovery analysis found that estimated CD14+ classical monocyte percentages above the mean correlated with shorter transplant-free survival times (hazard ratio, 1.82), but percentages of T cells and B cells did not.

The researchers then validated these results using samples from patients with idiopathic pulmonary fibrosis in two independent cohorts. In the COMET validation cohort, which included 45 patients with idiopathic pulmonary fibrosis whose monocyte counts were measured using flow cytometry, higher monocyte counts were significantly associated with greater risk of disease progression. In the Yale cohort, which included 15 patients with idiopathic pulmonary fibrosis, the 6 patients who were classified as high risk on the basis of a 52-gene signature had more CD14+ monocytes than the 9 low-risk patients did.

In addition, Ms. Scott and her collaborators looked at complete blood count values in the electronic health records of 45,068 patients with idiopathic pulmonary fibrosis, systemic sclerosis, hypertrophic cardiomyopathy, or myelofibrosis in Stanford, Northwestern, Vanderbilt, and Optum Clinformatics Data Mart cohorts.

Among patients in the COMET, Stanford, and Northwestern datasets, monocyte counts of 0.95 K/mcL or greater were associated with mortality after adjustment for forced vital capacity (HR, 2.47) and the gender, age, and physiology index (HR, 2.06). Data from 7,459 patients with idiopathic pulmonary fibrosis "showed that patients with monocyte counts of 0.95 K/mcL or greater were at increased risk of mortality with lung transplantation as a censoring event, after adjusting for age at diagnosis and sex" in the Stanford (HR, 2.30), Vanderbilt (HR, 1.52), and Optum (HR, 1.74) cohorts. "Likewise, higher absolute monocyte count was associated with shortened survival in patients with hypertrophic cardiomyopathy across all three cohorts, and in patients with systemic sclerosis or myelofibrosis in two of the three cohorts," the researchers said.

The study was funded by grants from the Bill & Melinda Gates Foundation, U.S. National Institute of Allergy and Infectious Diseases, and U.S. National Library of Medicine. Ms. Scott had no competing interests. Coauthors disclosed grants, compensation, and support from foundations, agencies, and companies.

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SOURCE: Scott MKD et al. Lancet Respir Med. 2019 Jun. doi: 10.1016/S2213-2600(18)30508-3.

FROM THE EVP/CEO

Opportunities for CHEST to broaden its reach across the globe

BY BOB MUSACCHIO, PHD

In order to have a greater impact on the way that lung diseases, critical care conditions, and sleep disorders are diagnosed and treated, CHEST has been actively expanding its reach and the way it plans, develops, and executes its international educational strategy.

Our recent congress in Bangkok, Thailand, was just the beginning of our plans to expand the CHEST brand and share our innovative education across the globe.

The congress held this past April served as a successful launchpad that included attendance of over 1,000 delegates who represented 57 countries and featured innovative and diverse educational opportunities that incorporated the best of the CHEST Annual Meeting, including interactive lectures, recent advances in clinical practice and science, guided poster presentations, and hands-on simulation opportunities.

The exceptional program is attributed to the partnership with the Thoracic Society of Thailand; the Chair, Dr. David Schulman; the faculty, for delivering such an innovative and engaging educational event; and many others who planned, supported, and participated in this impressive event.

This was CHEST's first venture into a new model designed around hosting one large congress outside of the United States and one smaller regional congress each year. This year, Athens, Greece, followed in June as the site of the regional congress. In subsequent years, we hope to increase the offerings and the options for these regional international events.

Dr. Musacchio

Newly announced, the CHEST Congress 2020 will be held in Bologna, Italy, June 25-27, in collaboration with the CHEST delegation from Italy, led by Dr. Francesco de Blasio. The program chairs for this event are Dr. de Blasio and Dr. William Kelly.

We are excited to broaden our international educational reach through this plan. By refining, growing, and building upon this new model and developing more live learning, hands-on simulation, CHEST gamification, and other interactive components, we continually provide the most cutting-edge learning opportunities available across the globe.

We are accomplishing this through partnering with global societies and CHEST delegations to identify unmet educational needs by region and patient base. Through this expansion, we hope to continue our fight to "Crush" lung disease wherever it exists.

CHEST faculty getting ready for the CHEST Congress 2019 Thailand, which was held in Bangkok, April 10-12.

CHEST NETWORKS

Biologics. NetWork name change. Rapid sequence intubation. Competitive bidding. Genomic classifier.

Airways disorders

Asthma biologics: which patients?

Biologic therapies targeting specific inflammatory pathways promise "precision" medicine for severe asthma. Because these therapies are expensive and have different mechanisms of action, appropriate patient selection is crucial. To date, the biologics have been primarily used in severe asthma.

Severe asthma has been defined as "asthma which remains uncontrolled on high-dose inhaled corticosteroids plus a second controller for the previous year or systemic corticosteroids (for 50% or more of the previous year) to prevent it from becoming uncontrolled, or which remains uncontrolled despite this therapy" (Chung, et al. *Eur Respir J.* 2014;43:[2]343).

Severe asthma is an infrequent to rare occurrence. Only 5% to 10 % of patients have severe asthma (Varsano, et al. *Respir Med.* 2017;123:131). Indeed, one study suggests that only 3.6% of patients meet criteria for it (Hekking, et al. *J Allergy Clin Immunol.* 2015;135[4]:896).

Dr. Conroy

Dr. Garay

Not all difficult to control asthma is severe. With aggressive management of comorbidities and appropriate assessment of medication adherence/inhaler technique, up to 50% of uncontrolled asthmatics can reach therapeutic goals with traditional stepwise inhaler-based therapies (Tay, et al. *J Allergy Clin Immunol Pract.* 2017;5[4]:956; Hekking, et al. *J Allergy Clin Immunol.* 2015;135[4]:896). Yet, incorrect inhaler technique (MDI and DPI) is unacceptably frequent and has not improved over the past 40 years (Sanchis, et al. *Chest.* 2016;150[2]:394). Furthermore, correct inhaler technique was found in only 15.5% of health-care providers and has worsened in recent years (Plaza, et al. *J Allergy Clin Immunol Pract.* 2018;6[3]:987).

After establishing appropriate diagnosis, control of comorbidities, proper inhaler technique, and medication adherence, evaluation of a severe asthmatic's inflammatory phenotype is necessary. Several phenotypes have emerged, including the severe allergic asthma phenotype and the severe eosinophilic asthma phenotype. Molecular phenotyping allows stratification into type–2–high vs type–2-low patients, which helps guide selection of the appropriate biologic. Options include: (1) anti-IgE (omalizumab); (2) anti-interleukin–5 (mepolizumab and reslizumab); (3) anti-interleukin-5 receptor alpha (benralizumab); and (4) anti-interleukin-4 receptor alpha and interleukin-13 (dupilumab).

Targeted biologics for specific severe asthma phenotypes may be cost effective long-term. However, long-term side effects need to be assessed and pharmaco-economic studies need to be performed.

Megan Conroy, MD
Steering Committee Fellow-in-Training

Stuart M. Garay, MD, FCCP
Steering Committee Chair

Clinical research and quality improvement

Anew, redefined, and enriched

CHEST Physician readers may not know that the Clinical Research NetWork recently changed its name to include quality improvement

(QI). Its new mission is "to provide a forum for clinical research, QI, research ethics, and regulatory aspects, as topics of multidisciplinary discussion and collaboration." Medical education has become a natural addition to our NetWork's scope,

Dr. Ioachimescu

as this field of scholarly activity has emerged and grown tremendously in the past decade. Interestingly, the number of session submissions to CHEST 2019 increased by a whopping 32% vs 2018, while our NetWork saw an even more impressive increase of 42% in submissions deemed Clinical, Education Research, or QI.

The initial concept of a CHEST Clinical Research NetWork was narrower, aiming to fill gaps between our members' interests and activities with those of pharmaceutical industry partners and equipment and device manufacturers. Its scope evolved, and our NetWork became the home of all clinical research endeavors not pinned to a specific condition, disease class, or membership category.

QI emerged in other industries long ago, using scientific methods and known to be foundational for any organization's capacity to survive in competitive environments, become more efficient, satisfy customers, improve outcomes, and develop better work flows and conditions for employees and business partners.

If the QI world strives to achieve certainty with confidence levels less than 0.0001, it is interesting that in our scientific quest we settle for *P* less than .05. Self-indulgence? Simplistically speaking, are we tolerating "defect rates" of 5%, while others aim for 6 sigma thresholds? These are a few thoughts on how health care can learn from other industries and apply more stringent standards for scholarly activities in clinical research, education, and QI.

In conclusion, while it continues to strive to build the infrastructure of future CHEST clinical research nodes for randomized or observational multicentric studies, Clinical Research and QI NetWork enthusiastically embraces the fields of medical education and QI into its enriched activity scope and scale.

Octavian C. Ioachimescu, MD, PhD, FCCP
Steering Committee Member

Critical care

Rapid sequence intubation

Casey and colleagues recently published a study (*N Engl J Med.* 2019;380[9]:811) that challenges the long-held view that rapid sequence intubation (RSI) should not include ventilation attempts between induction and laryngoscopy. Airway management purists will say that true RSI is pre-oxygenate, give a sedation agent followed immediately by a paralytic agent, and immediate laryngoscopy as soon as the patient is paralyzed. However, RSI has come to mean the use of a sedation agent and a paralytic agent without specific timing of when to give the paralytic.

Dr. Gaillard

Purists would also say RSI is done for patients who are at a high risk for aspiration. In this study, the amount of subjectively reported aspiration was actually lower in the YES BVM group: 2.5% vs 4.0%. The presence of a new opacity on chest radiograph within 48 hours was 16% vs 15%, suggesting that there is no significant difference in the incidence of aspiration.

In this study, 40% in the NO BVM group and 30% in the YES BVM group had O_2 desaturations below 90%. These statistics highlight the fact that it is imperative to pre-oxygenate all patients who will undergo intubation. Critically ill patients have little reserve. These patients are on the steep portion of the oxygen dissociation curve. The saturations will drop quickly. It is better to avoid any desaturation, if possible.

This study demonstrates that bag-mask ventilation between induction and laryngoscopy can help prevent severe desaturation with a number needed to treat to prevent one severe hypoxic event is nine.

John Gaillard, MD, FCCP
Steering Committee Member

Home-based mechanical ventilation and neuromuscular disease

Pressures of competitive bidding process

Advancements in invasive and non-invasive ventilator technology have allowed patients with neuromuscular conditions and severe COPD to transition from institutional care to living at home. Ventilator support is reserved for severe or progressive respiratory impairment where interruption would lead to serious negative consequences. Access to this technology does entail significant cost, as monthly rental fees range from $660 to $1,352, and yearly ventilator claims for chronic respiratory failure have increased from 29% in 2009 to 85% in 2015 (US Dept HHS, OIG Data brief 2016). There is a current proposal to include home mechanical ventilators with oxygen and other services in competitive bidding programs (CBP). Since oxygen was included in CBP, access to liquid oxygen systems and payments for oxygen have decreased significantly. Of patients using home oxygen since July 1, 2016, 59% reported difficulties with access to oxygen-related equipment and services (American Association for Respiratory Care: Comment on Federal policies, aarc.org).

Dr. Brown

Ventilator-dependent patients should not be subjected to the pressures of CBP when trying to obtain the equipment, supplies, and access to experienced medical providers that are necessary to remain in their homes. Beyond denying ventilatory support to some, CBP may also result in other unintended consequences, including the increased use of otherwise avoidable tracheostomies to ensure coverage for appropriate services. CHEST, including the Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork and other patient groups, has advocated that home mechanical ventilators should be permanently excluded from the CBP to protect these fragile and vulnerable patients.

Jeanette Brown, MD, PhD
Steering Committee Member

Interstitial and diffuse lung disease

New genomic classifier

A confident diagnosis of idiopathic pulmonary fibrosis (IPF) relies on the radiographic pattern of usual interstitial pneumonitis (UIP), although in some cases, histologic confirmation is warranted. Transbronchial biopsy (TBBx) does not provide adequate tissue for diagnosis, thus patients are subjected to the risk of a surgical biopsy. A promising new test can increase confidence in the diagnosis of IPF. The Envisia Genomic Classifier (Veracyte) is a recently approved test to aid in the diagnosis of IPF. It utilizes 190 genes and RNA sequencing, combined with machine learning, to create an algorithm that determines the presence of UIP on samples derived from TBBx.

Dr. D'Annunzio

A proof-of-principle study described the characteristics of the genomic classifier in distinguishing UIP for 53 training subjects and 31 test subjects. To ensure validation, this new test was compared with a diagnosis determined by histopathologic review from expert pathologists. Specificity was 86% and sensitivity 63% in distinguishing UIP vs non-UIP patterns. Although false-negatives were a concern due to IPFs heterogeneous involvement of the lung, combining multiple specimens from a single patient increased accuracy.

The recently-published BRAVE study was a validation and utilization study, proving the test's success in identifying UIP on TBBx samples. The test was again compared with diagnostic histopathology, demonstrating 88% specificity and 70% sensitivity. In addition, two multidisciplinary teams had an 86% agreement on diagnoses when using pathology vs the genomic classifier. The classifier is commercially available and is covered by Medicare in the United States.

As with all new technology, it is expected that its use will increase in the future and that we will learn more about how, and in whom, to best utilize this tool.

Samantha D'Annunzio, MD
Steering Committee Member

References

Pankratz DG, et al. *Ann Am Thorac Soc.* 2017;14[11]1646.

Raghu G, et al. *Lancet Respir Med.* 2019 Jun;7(6):487.

In memoriam

CHEST has been notified of the following deaths. We extend our sincere condolences.

John W. Thomas, MD (2018)
Frederick J. Curley, MD (2018)

Fill your day in New Orleans

No matter if you're only in New Orleans during #CHEST2019 for a day or for the entire meeting, we've got you covered on how to spend your time in the Big Easy outside of sessions and CHEST events!

CHEST® Annual Meeting 2019

Rise and shine! If breakfast is the most important meal of the day, we've got the perfect way to start your morning before heading over to the Ernest N. Morial Convention Center to begin a day of learning. For a quick bite, try the ever popular Cafe du Monde Riverwalk next to the convention center for a light breakfast of beignets and café au lait, or Fulton Street Cafe.

Lunchtime: For something a little more hearty, head to Green Goddess in the French Quarter for southern comfort food. There's something for everyone, as you'll even find some vegan dishes on the menu. If you have time for a longer mid-day break, check out a Garden District Tour, Steam Boat on the River, or relax in Jackson Square.

Evening: You've had a long day of sessions, lectures, and exploring the exhibit hall, and now you want to wind down with a good meal (and maybe a drink!). For a slower vibe and space to linger and enjoy yourself, take an Uber/Lyft over to La Petite Grocery on Magazine Street for some tasty, traditional dishes.

If you're a night owl or looking for a late-night activity with a group of your friends and peers, there are plenty of places to find a cocktail on Bourbon Street, or listen to live jazz music along Frenchman Street.

There are many more things you can check out in New Orleans, and we hope you enjoy your stay during CHEST 2019.

**Note: If you're staying in the hotel block near the convention center, many of the attractions, including the Convention Center, will be a short walking distance. Otherwise, we suggest taking an Uber or Lyft to reach your destination.*

CHEST Clinical Perspectives™ explores the emerging field of precision medicine

For clinicians seeking to provide a pathway to treatment or diagnosis that is individualized to the patient, a recent study found that the issues go beyond awareness or a patient's degree of comfort – there remains the question of something as simple as: what should we call it?

Clinicians remain uncertain whether to name the new field precision or personalized medicine according the new *CHEST Clinical Perspectives*™ white paper, "Precision Medicine: Adoption of Emerging Methods of Evaluation and Therapy." A survey of leading community clinicians from among CHEST membership found that only 35 % called tailoring medical treatment to the individual characteristics of each patient "precision medicine," with 24% preferring "personalized" medicine. Thirty-six percent of respondents used the terms interchangeably.

Beyond the communication issues, the study found that most clinicians surveyed did not know enough about precision medicine to adopt it into their practice. Those surveyed reported that they wanted to see more published studies on the effectiveness of the newly available tools before discussing these options with their patients.

The majority of the respondents were general pulmonologists with intensivists and interventional pulmonologists also responding. The study was led by Nichole T. Tanner, MD, MSCR, FCCP, of the Medical University of South Carolina. Dr Tanner will be hosting a webinar to review the conclusions of this paper at 10:00 AM CT on Tuesday, July 30.

More information about *CHEST Clinical Perspectives*™, part of the CHEST Analytics program, can be found at insights.chestnet.org. To suggest a topic to be covered in a future issue, contact Linda Tomczynski, ltomczynski@chestnet.org or +1 (224) 521-9593. Register today at https://hubs.ly/H0jqCGb0.

This month in the journal *CHEST*®

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BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief

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ORIGINAL RESEARCH

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Pulmonary Edema Following Initiation of Parenteral Prostacyclin Therapy for Pulmonary Arterial Hypertension: A Retrospective Study
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Lung Allocation Score Thresholds Prioritize Survival After Lung Transplantation
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EVIDENCE-BASED MEDICINE

Chronic Cough and Gastroesophageal Reflux in Children: CHEST Guideline and Expert Panel Report
By Dr. A. B. Chang, et al.

Environmental Scan: Drivers of change in health care

Chest physicians are witnessing a revolution within the environment in which they practice. Information technology, changing consumer behavior, and the social imperative to contain costs are coming together to transform health care.

Innovation in the prevention, diagnosis, and treatment of health-related issues is being fueled by the emergence of accessible and affordable technology-based solutions and changes in patient approaches to health care. Consumers and employers are increasingly motivated to look for cost-effective options for health in care delivery and for economical access to innovations.[1] Organizations will need to respond with a strategy that aligns with the changing environment and position physicians to lead these trends in the direction of improved patient care.[2]

CHEST® INSPIRATION: Pacing the Future

Enabling technologies like electronic health records, blockchain, and artificial intelligence will increase connectivity among all the stakeholders in the health-care system. The exponential increase in connectivity means growing engagement of health systems, health plans, patients, and families in all aspects of health care. For health-care providers, these technologies will mean an acceleration of the requirement to generate data in clinical settings and utilize data for clinical decision making. Easily available data on outcomes and, most importantly, cost of treatment will be expected at point of service.[3]

Access to information will continue to empower consumers to take an active role in their own health care. More patients will be comfortable with delivery of some health care via digital devices, apps, and virtual access to treatment. The market will respond with technology that helps consumers navigate health-care systems, explore options, and communicate directly with providers. The use of apps and virtual encounters is expected to transform the role of primary care providers: patients will increasingly utilize nonphysician resources in outpatient settings, bypassing primary care physicians and reaching out to specialty care as needed.[4]

David A. Schulman, MD, FCCP, Professor of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University School of Medicine, Atlanta, and Editor in Chief of *CHEST Physician*, has seen the transformation of patient behavior and attitudes in his own practice.

"In general, they have done far more research about their health problems before seeking my counsel than patients did previously. Many use the internet not just to read about their symptoms and diseases, but also to connect with others having similar issues, sharing experiences, treatments, outcomes, and emotions; in some ways, this is the new 'crowdsourcing' of medicine."

Patients who do their own "research" can present a challenge for physicians. Dr. Schulman noted, "I am often surprised about the misconceptions about disease that derive from information gleaned from a web-based source. One need not look any farther than the groundswell of misinformation being spread about vaccinations to see the potential downside of the pervasive availability of medical 'facts' online. Since we are unlikely to convince our patients to avoid the online milieu entirely, our role as health-care providers is to help our patients process and appropriately weigh the information that they receive, potentially partnering with our national societies to help curate such information."

Dr. Schulman's approach to the potential of patient misinformation is to initiate almost all discussions with patients with the question "Have your read or seen anything about this condition?" He said, "It is rare for patients to answer negatively. And listening to them speak about their understanding of their disease provides me with invaluable information about how the remainder of our visit should be spent. Do we need to correct misunderstandings? Are there gaps in the explanation that I can fill? Can we move directly into a conversation about treatment options? Can I provide you with some additional resources that might help to further your knowledge about the condition?"

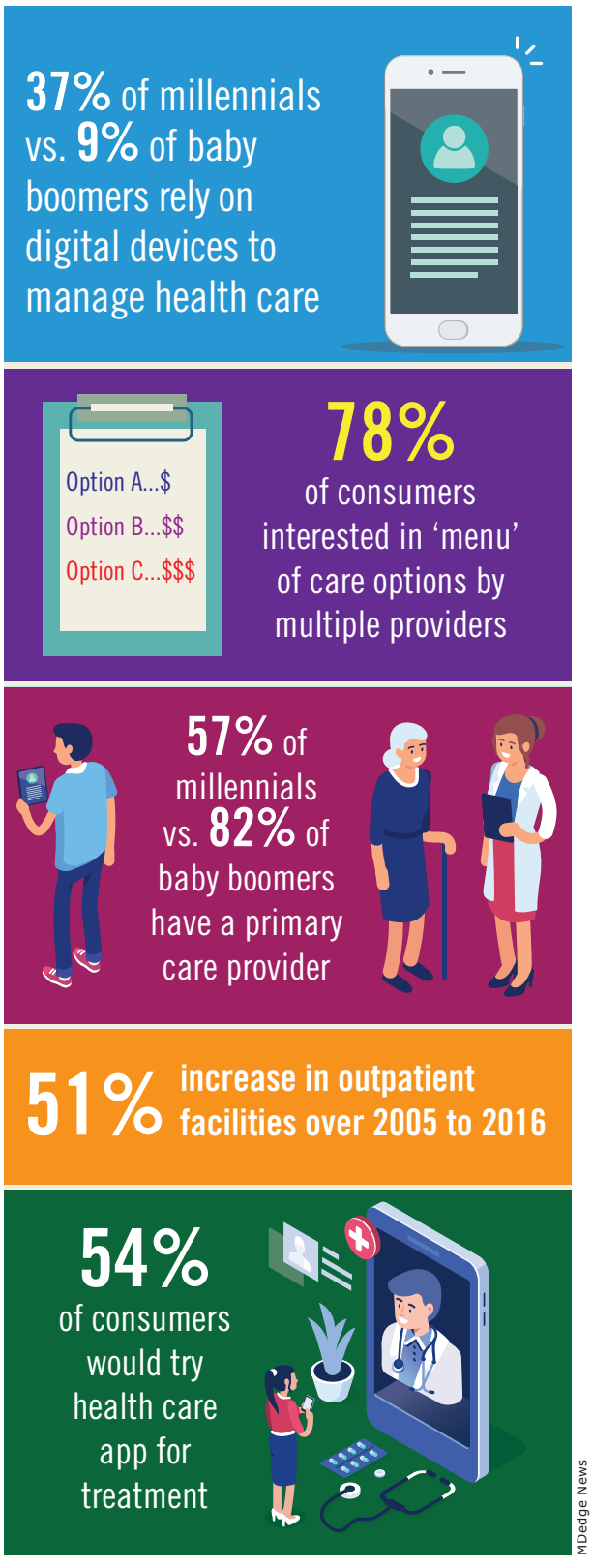
Generational factors will play a big role in health-care demand and delivery. Health-care companies are already building lower cost delivery models to capture the millennial market.4 Cost-saving digital tools and virtual contacts are currently most commonly used by younger patients.[5] Physicians need to understand and be a part of this trend, Dr. Schulman argued. "We should embrace telemedicine and mobile applications to collect data from the patients in their day-to-day lives. While insurance coverage of telemedicine is far from universal at the moment, and the reliability of mobile applications is highly variable, we know that a growing number of our patients are already relying on their digital devices to manage their health. In much the same way that we will need to help patients evaluate online information, we should work with our national societies to support the creation of tools that will allow us to collect data in the home environment in a more robust and reliable fashion."

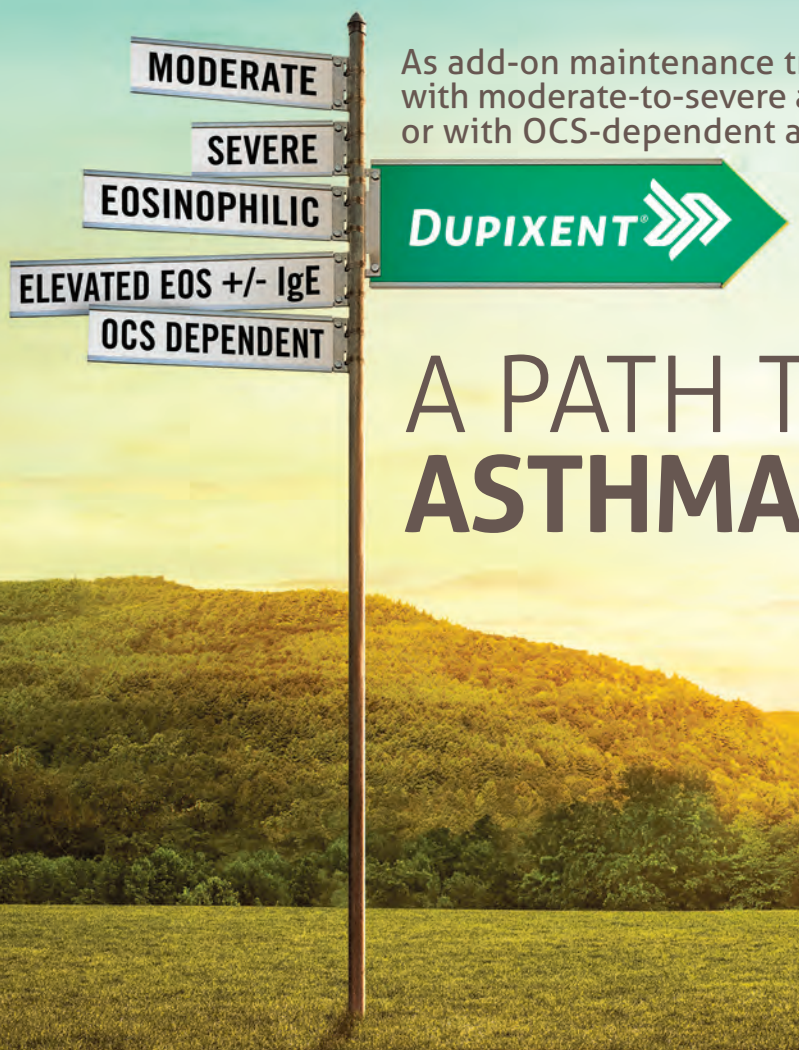
The proportion of the US population over the age of 65 is increasing yearly.[6] Six out of 10 Americans live with a chronic illness, such as heart disease or diabetes. These and other chronic diseases are the leading drivers of the $3.3 billion annual health-care costs.[7] Cost containment for these older patients and those with chronic illness will involve a focus on quality and outcomes data, a drive to deliver treatment in lower cost outpatient settings, and an acceleration of the adoption of value-based models currently underway.[8]

Taken together, these trends will mean a growing digital interface between physician and patient, a more active consumer-patient, and the availability of a vast array of new tools to access and manage health-care data.

Continued on page 42

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.





As add-on maintenance treatment for patients (12+ years) with moderate-to-severe asthma with an eosinophilic phenotype, or with OCS-dependent asthma regardless of phenotype

A PATH TO **ASTHMA CONTROL**

A NOVEL BIOLOGIC THAT INHIBITS IL-4 AND IL-13 SIGNALING, TWO OF THE SOURCES OF INFLAMMATION IN ASTHMA[1,a]

[a] **The mechanism of dupilumab action in asthma has not been established.**

INDICATION

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

LIMITATION OF USE

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

IMPORTANT SAFETY INFORMATION

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

WARNINGS AND PRECAUTIONS

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

Eosinophilic Conditions: Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia, which may be associated with a reduction of oral corticosteroids. Cases of eosinophilic pneumonia and of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

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

LEARN MORE AT *DUPIXENTASTHMAHCP.COM*

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **81%**

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

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

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **430 mL**

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

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

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

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

DUPIXENT® (dupilumab) Injection
200mg · 300mg

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

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

↑ 430 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

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

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

↑ 390 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

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

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

IMPORTANT SAFETY INFORMATION

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

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

USE IN SPECIFIC POPULATIONS

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

DUPIXENT® (dupilumab) Injection
200mg · 300mg

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

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

70%

REDUCTION IN OCS DOSE

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

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

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

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

59%
REDUCTION

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

220 mL
IMPROVEMENT

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

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

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

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

References: 1. DUPIXENT Prescribing Information. March 2019. **2.** Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. **3.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485.

SANOFI GENZYME

REGENERON

US-DAS-1450(1)

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

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

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

Limitation of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of keratitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

5.3 Eosinophilic Conditions

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

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

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

5.6 Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Conjunctivitis and Keratitis *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT plus TCS to placebo plus TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4)

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 1: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reaction	DUPIXENT Monotherapy[a]		DUPIXENT + TCS[b]	
	DUPIXENT 300 mg Q2W[c] N=529 n (%)	Placebo N=517 n (%)	DUPIXENT 300 mg Q2W[c] + TCS N=110 n (%)	Placebo + TCS N=315 n (%)
Injection site reactions	51 (10)	28 (5)	11 (10)	18 (6)
Conjunctivitis[d]	51 (10)	12 (2)	10 (9)	15 (5)
Blepharitis	2 (<1)	1 (<1)	5 (5)	2 (1)
Oral herpes	20 (4)	8 (2)	3 (3)	5 (2)
Keratitis[e]	1 (<1)	0	4 (4)	0
Eye pruritus	3 (1)	1 (<1)	2 (2)	2 (1)
Other herpes simplex virus infection[f]	10 (2)	6 (1)	1 (1)	1 (<1)
Dry eye	1 (<1)	0	2 (2)	1 (<1)

[a] Pooled analysis of Trials 1, 2, and 4.
[b] Analysis of Trial 3 where subjects were on background TCS therapy.
[c] DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.
[d] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.
[e] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.
[f] Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 52 (Trial 3)

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject). The safety profile of DUPIXENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Adolescents with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

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

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

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

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

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

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.
[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*.

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

Specific Adverse Reactions

Conjunctivitis

During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Warnings and Precautions (5.2)]*.

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group

(1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

Hypersensitivity Reactions

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

Eosinophils

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

Cardiovascular (CV)

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

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), CV thromboembolic events (CV deaths, non-fatal MIs, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 6% of subjects with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses and ~2% had neutralizing antibodies.

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

Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

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

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

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

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

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

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

Risk Summary

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults *[see Adverse Reactions (6.1) and Clinical Studies (14.2) in the full prescribing information]*. Safety and efficacy in pediatric patients (<12 years of age) with atopic dermatitis have not been established.

Asthma

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

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

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

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

10 OVERDOSE

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

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUPIXENT and each time the prescription is renewed as there may be new information they need to know.

Pregnancy Registry

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

Administration Instructions

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

Hypersensitivity

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

Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop *[see Warnings and Precautions (5.2)]*.

Eosinophilic Conditions

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

Not for Acute Asthma Symptoms or Deteriorating Disease

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

Reduction in Corticosteroid Dosage

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

Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians *[see Warnings and Precautions (5.6)]*.

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A distinguished 14-year editorship


Dr. Richard S. Irwin

In 1968, Richard S. Irwin, MD, Master FCCP, graduated from Tufts University School of Medicine. After completing medical residency training at the Tufts-New England Medical Center and pulmonary training at Columbia Presbyterian Medical Center, he has been practicing in pulmonary and critical care medicine for the last 50 years.

It was in 1979 that he became a CHEST member; in 2003-2004, he served as President of CHEST; and he has been actively involved as a CHEST leader throughout his career, serving on every major CHEST committee. But Dr. Irwin's most beloved position has been as Editor in Chief of the journal *CHEST*®, a journey that began in 2005 – a position that he has filled for 14 years and that which he has recently stepped down from in June 2019. What better description of those 14 years at the helm of one of the most recognized and respected journals in chest medicine than to hear it straight from the Editor in Chief himself. In the June 2019 issue of the journal *CHEST*®, Dr. Irwin shares his thoughts in this Commentary: "On Being the Editor in Chief of the journal *CHEST*: 14 Memorable Years." Don't miss it! https://journal.chestnet.org.

Continued from page 35

- Delivery of procedures and services will trend from physicians to other members of the health-care team and to lower cost, outpatient settings.[9]
- Health-care systems will ramp up investment in products and services that improve outcomes and cost effectiveness.[10]
- Increased regulatory requirements and new payment models mean an ever-growing utilization of information technology by providers to fulfill data imperatives.[11]
- Physicians will have an increased need for tools that prioritize costs and outcomes data at the point of care.[12]
- Integration of data from new technologies will touch every aspect of health-care delivery with the objective of improving outcomes and, in turn, reducing costs.[13]
- Changing consumer attitudes toward delivery of care will be based on a growing familiarity of patients with a digital or virtual interface with providers, facility with health-care apps, and preference for a menu of options for health-care delivery.[14]

Dr. Schulman concluded, "We can no more expect our patients to ignore the full panoply of medical information on the internet and digital tools on their mobile devices than we can tell the tide not to come in. The die is cast; this is the world within which we must ply our trade. By identifying best practices and sharing our successes, we can come through this revolution better for the experience."

1. https://www.modernhealthcare.com/article/20181220/NEWS/181229992/number-of-outpatient-facilities-surges-as-industry-values-more

2. https://www.accenture.com/us-en/insights/health/digital-health-tech-vision-2018

3. https://www.accenture.com/us-en/insights/health/digital-health-primary-care

4. PcW Health Research Institute: Top health industry issues of 2019

5. https://www.accenture.com/us-en/insights/health/digital-health-primary-care

6. https://www.census.gov/newsroom/press-releases/2017/cb17-100.html

7. https://www.cdc.gov/chronicdisease/index.htm

8. https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/health-care-current-december4-2018.html

9. PcW Health Research Institute Top health industry issues of 2019: The New Health Economy comes of age

10. https://www.accenture.com/us-en/insights/health/digital-health-tech-vision-2018

11. https://www2.deloitte.com/insights/us/en/industry/life-sciences/medtech-research-and-development-innovation.html

12. https://www2.deloitte.com/insights/us/en/industry/health-care/volume-to-value-based-care.html

13. https://www2.deloitte.com/insights/us/en/industry/health-care/volume-to-value-based-care.html

14. https://www.accenture.com/us-en/insights/health/digital-health-primary-care

Note: Background research performed by Avenue M Group.

SLEEP STRATEGIES

Restless legs syndrome: Update on evaluation and treatment

BY MARK J. BUCHFUHRER, MD, FCCP, FAASM

Restless legs syndrome (RLS) is a very common disease affecting about 10% of Caucasian adults with about one third of them having RLS symptoms severe enough to require treatment.

Although many patients still go undiagnosed or misdiagnosed, the diagnosis is easily established with the five diagnostic criteria that are simplified by the acronym URGES:

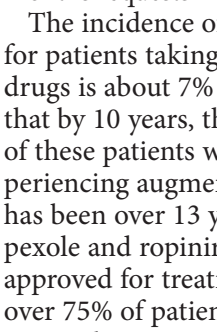
1. ***U**rge* to move the legs associated with unpleasant leg sensations.
2. ***R**est* induces symptoms.
3. ***G**ets* better with activity.
4. ***E**vening* and nighttime worsening.
5. ***S**olely* not accounted by another medical or behavioral condition.

The diagnosis is based completely upon the history. However, supplemental tests can be helpful to rule out underlying conditions that increase the risk of RLS. Routine lab tests, such as serum creatinine (to rule out renal disease), TSH (to rule out thyroid disease), and a CBC/ferritin/iron with transferrin saturation (to rule out low iron stores) should be ordered if not done recently.

A polysomnographic sleep study should not be ordered unless there is a strong suspicion that sleep apnea is present. Even very frequent PLM (periodic limb movements) are not that helpful in confirming the diagnosis of RLS since they are nonspecific and often occurring with drug treatment (SSRIs, SNRIs) and many medical conditions such as sleep apnea, narcolepsy, and REM behavior disorder.

The paradigm for treating RLS has been presented in the consensus article published in 2013 (Silber MH, et al. *Mayo Clin Proc.* 2013 Sep;88[9]:977). Since 2013, there has been a gradual shift of that paradigm that recommended starting an approved dopamine agonist (pramipexole, ropinirole, or rotigotine) or an alpha-2-delta ligand (gabapentin enacarbil, gabapentin, or pregabalin) as first-line treatment. Although dopamine agonists provide excellent relief of RLS symptoms initially, with time, they tend to markedly worsen RLS. This process is called RLS augmentation and has become one of the most common causes of refractory RLS and difficult-to-treat patients.

RLS augmentation typically onsets a few months to several years after starting a short-acting dopamine agonist (DA) like pramipexole or ropinirole. It presents with symptoms occurring a few hours earlier than prior to starting the medication, symptoms becoming more intense with less rest time needed to trigger RLS symptoms, drugs becoming less effective both in effectiveness and duration of action, and spread of symptoms to other body parts (arms, trunk, and even head). The majority of physicians mistake this worsening of RLS for the natural progression of the disease and, thus, increase the dose of the DA, which provides temporary improvement. Further increases become progressively necessary until the patient is receiving very large doses, often exceeding 10 times the FDA maximum recommended doses. Eventually, further dose increments provide minimal additional benefit, leaving patients with severe, around the clock RLS symptoms causing extreme misery. To be more aware of augmentation, physicians should consider augmentation may be occurring whenever a patient who has been receiving a regimen of stable dopamine agonist treatment for at least 6 months requests more medication.


Dr. Buchfuhrer

The incidence of augmentation for patients taking short-acting DA drugs is about 7% to 8% per year so that by 10 years, the vast majority of these patients with RLS are experiencing augmentation. Since it has been over 13 years since pramipexole and ropinirole have been approved for treating RLS, currently, over 75% of patients referred to national RLS experts are referred due to augmentation (although the actual referral diagnosis is often "refractory RLS"). Despite the concerns about augmentation, the short-acting DA drugs are by far the most commonly prescribed medications

for initial treatment of RLS.

To help educate doctors about RLS augmentation, a consensus article was published in 2016 promoting guidelines for the prevention and treatment of RLS augmentation (Garcia-Borreguero D, et al. *Sleep Med.* 2016;21:1-11). Since augmentation occurs only with dopaminergic drugs (with the exception of tramadol), considering the use of nondopaminergic drugs for first-line therapy of RLS would dramatically decrease the occurrence of augmentation. This is a clear shift in the paradigm of choosing equally amongst the approved RLS drugs.

Unless contraindicated, the alpha-2-delta drugs should be the first consideration for treating new RLS patients. These drugs can be as effective as the DA drugs but cannot cause augmentation and, also, do not cause impulse control disorders, which occur with the use of DAs. Furthermore, they reduce insomnia and anxiety that are both associated with RLS. The use of these drugs may be limited by their side effects, which include CNS depressive effects (sedation, dizziness, decreased balance or cognition) or depression.

When the alpha-2-delta ligands can't be used due to lack of efficacy, side effects, or cost, the DA drugs may then be appropriate. The rotigotine patch has the lowest incidence of augmentation, especially at the approved doses of up to 3 mg. If the rotigotine patch cannot be used (most often due to skin side effects or cost), then the short-acting DA drugs may be employed. Augmentation may be prevented or significantly delayed by starting these drugs at their lowest dose (.125 mg for pramipexole and .25 mg for ropinirole) and increasing the dose as little as possible, definitely not exceeding the approved RLS limits of .5 mg for pramipexole and 4 mg for ropinirole. My personal suggestion is not to exceed .25 mg for pramipexole and 1 mg for ropinirole, as augmentation is dose-related but may occur at even the lowest doses. When patients need and request increased treatment for their RLS, rather than increasing the dose of the DA, instead, consider adding other medications, such as the alpha-2-delta ligands or even low dose opioids.

Managing augmentation is typically a very challenging problem for both the physician and patient; this is described in detail in the augmentation article referenced previously. Decreasing, or better yet eliminating, the short-acting DA is the preferred method for treating augmentation. However, upon elimination of the DA, there is a short period of 1 to 4 weeks (average of 10-12 days) when the RLS symptoms get dramatically worse. Patients typically experience extremely severe RLS symptoms around the clock and may not be able to sleep at all until the RLS calms down. Most often, only low dose opioid treatment will enable them to get through this transition. The augmentation article (with its algorithm) may help physicians manage augmentation, but patients with severe augmentation may need referral to an RLS specialist who is experienced in this area and who is comfortable managing the disease with opioids.

Low iron levels are often associated with RLS, cause RLS symptoms to worsen, and increase the risk of augmentation (Allen RP, et al, and the International Restless Legs Syndrome Study Group. *Sleep Med.* 2018;41:27). We typically suggest that patients with ferritin levels under 100 mcg/L should get supplemental iron. However, oral iron absorption is very limited when the patient's ferritin is above 50 mcg/L and, most patients may require IV iron to improve their RLS symptoms. There are several IV iron preparations but only iron dextrose, iron carboxymaltose, and ferumoxytol are effective. When the ferritin level is increased to over 200 mcg/L, RLS symptoms may be dramatically improved.

With the currently available treatment options, most patients should have their RLS symptoms well controlled without developing augmentation.

Dr. Buchfuhrer is with Stanford University, Department of Psychiatry and Behavioral Sciences in the School of Medicine, Division of Sleep Medicine, Stanford, CA.

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