Go to **MDedge.com/CHESTPhysician** for the latest news on the coronavirus pandemic.

COMMENTARY
Revised sarcoidosis guidelines offer important updates. // **10**

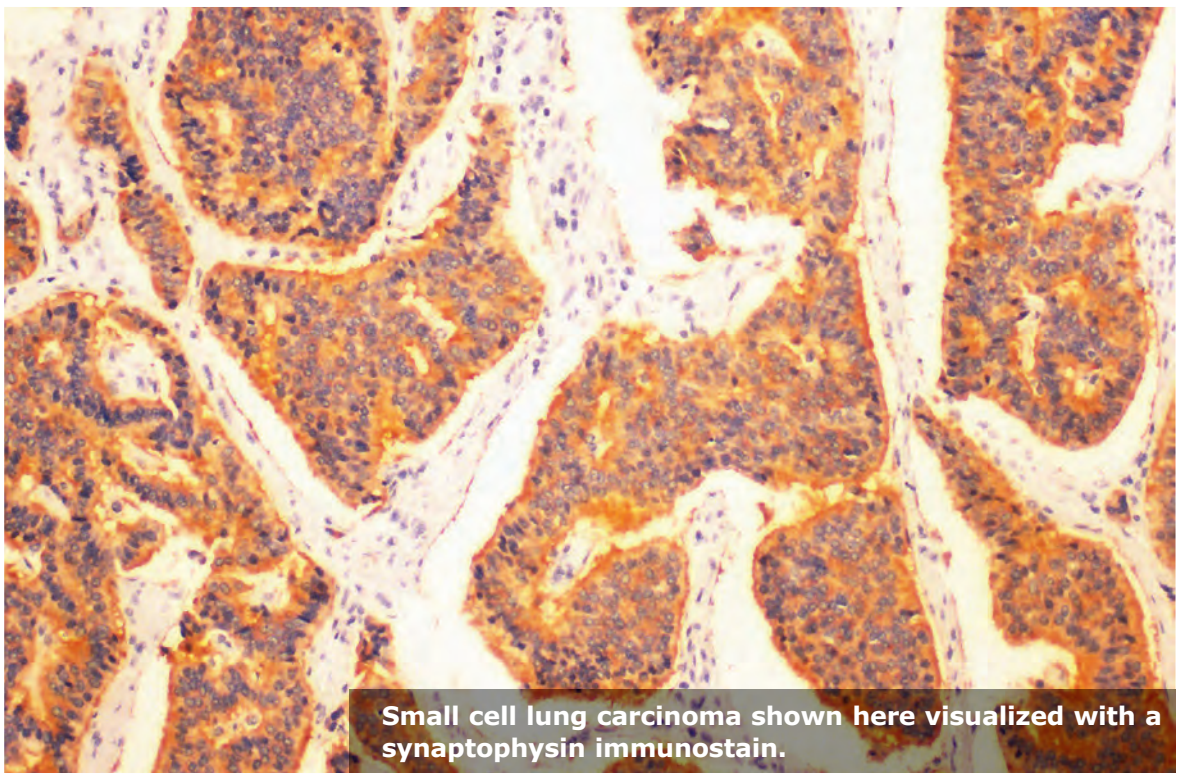
PEDIATRIC PULMONARY
The pandemic has worsened the childhood obesity crisis. // **14**

BUSINESS OF MEDICINE
Portals aid patient access but cause docs headaches. // **34**

VOL. 16 • NO. 11 • NOVEMBER 2021

CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Wikimedia Commons/Yale Rosen/CC-BY-SA-2.0

Small cell lung carcinoma shown here visualized with a synaptophysin immunostain.

‘Unprecedented’ 3-year sustained survival with lung cancer tx combo

BY SHARON WORCESTER
MDedge News

The overall survival benefit with durvalumab plus etoposide and cisplatin/carboplatin versus EP alone for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC) as demonstrated in the phase 3 CASPIAN trial was sustained beyond 3 years, according to a planned exploratory analysis.

The durable overall survival (OS) benefit and the well-tolerated safety profile of the durvalumab with EP therapy further establishes the combination as the standard of care for the first-line treatment of ES-SCLC, Luis Paz-Ares, MD, reported at the 2021 European Society for Medical Oncology Congress (abstract LBA61).

At 3 years, there is more than three times the survival in patients with durvalumab and EP versus EP, and at the same time, the adverse-event profile continues to be favorable,” said Dr. Paz-Ares of Universidad Complutense & Ciberonc, Madrid.

This is the longest follow-up reported to date for a phase 3 trial of a programmed death–ligand 1 inhibitor and EP in this setting, he said.

The CASPIAN trial included 805 treatment-naive patients with ES-SCLC who were randomized 1:1:1 to receive 1,500 mg of durvalumab with EP every 3 weeks, 1,500 mg of durvalumab at 75 mg of tremelimumab and EP every 3 weeks, or EP

CANCER TREATMENT COMBO // *continued on page 7*

New COVID-19 pill: ‘Game changer’ or just one more tool?

BY KATHLEEN DOHENY
MDedge News

Soon after Merck announced that it would ask federal regulators for emergency use authorization (EUA) for its auspicious new COVID-19 pill, the accolades began.

Former Food and Drug Administration chief Scott Gottlieb, MD, told CNBC the drug was “a profound game changer.” Top infectious disease expert Anthony S. Fauci, MD, called the early data “impressive.” The World Health Organization termed it “certainly good news,” while saying it awaits more data.

Merck, partnering with Ridgeback Biotherapeutics on the investigational oral antiviral medicine molnupiravir, plans to submit applications to regulatory agencies worldwide, hoping to deliver the first oral antiviral medication for COVID-19.

Interim clinical trial results show that the drug may slash the risk for hospitalization or death by

COVID-19 PILL // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM THE CHEST FOUNDATION

CHEST Foundation 2021 Grant Recipients

Pages 26-27

CHEST Physician
10255 W Higgins Road,
Suite 280
Rosemont, IL 60018

CHANGE SERVICE REQUESTED

PRSRT STD
U.S. POSTAGE
PAID
HARRISBURG PA
PERMIT 500

Rx

Why we write Esbriet

Your patients trust you. That's why you trust Esbriet for efficacy, safety, and tolerability.

INDICATION

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

SELECT IMPORTANT SAFETY INFORMATION

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

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

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

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

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

Drug Interactions:

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

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

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

Genentech
A Member of the Roche Group

AN IPF TREATMENT BACKED BY EXPERIENCE

Used in more than 60 countries worldwide for the treatment of idiopathic pulmonary fibrosis (IPF)[1]*

MORE THAN

136,000

PATIENT-YEARS

were derived from the volume of global sales of Esbriet and the estimated total amount taken by patients with IPF worldwide, from February 2011 through February 2019[1]

>5 YEARS

IN CLINICAL TRIALS[2]

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

Demonstrated safety and efficacy

In ASCEND and CAPACITY 004, Esbriet delayed disease progression by slowing lung function decline vs placebo[2,3]

In CAPACITY 006, no statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed[2,4]

Serious AEs, including elevated liver enzymes and drug-induced liver injury, photosensitivity reactions, and GI disorders, have been reported with Esbriet[1]

Learn more at **EsbrietHCP.com**

*Countries include Albania, Argentina, Australia, Austria, Belgium, Bulgaria, Brazil, Canada, Chile, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong (special administrative region), Hungary, Iceland, Ireland, Israel, Italy, Kosovo, Kuwait, Lithuania, Luxembourg, Macao (special administrative region), Malaysia, Malta, Montenegro, Myanmar, the Netherlands, New Zealand, Norway, Oman, Qatar, Paraguay, Poland, Portugal, Peru, Romania, Russia, Saudi Arabia, Serbia, Singapore, Spain, Slovakia, Slovenia, Sweden, Switzerland, Turkey, Ukraine, the United Arab Emirates, the United Kingdom, the United States, and Uruguay.[1]

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.

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

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

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

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

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

Study design: 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).[2] 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.[2,3] 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.[2,4] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[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).[2] **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.[2]**

References: 1. Data on file. Genentech, Inc. 2019. **2.** Esbriet Prescribing Information. Genentech, Inc. July 2019. **3.** 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. **4.** 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.

Esbriet® (pirfenidone) tablets 267 mg 801 mg

Once-daily poziotinib shows efficacy in NSCLC

BY WALTER ALEXANDER
MDedge News

Once-daily dosing of poziotinib shows clinically meaningful efficacy for patients with treatment-naive non–small cell lung cancer (NSCLC) HER2 exon 20 mutations, according to results of the ZENITH20 trial presented at the 2021 European Society for Medical Oncology Congress. Tumor reductions, stated lead author Robin Cornelissen, PhD, MD, Erasmus University, Rotterdam, the Netherlands, were seen in 88% of patients.

EGFR and HER2 exon 20 insertion mutations are rare subsets accounting for about 10% each of all mutations and 2%-4% each in NSCLC. "There is no approved therapy for either treatment-naive or previously treated NSCLC with HER2 exon 20 mutations,"

Dr. Cornelissen said in a virtual oral presentation (abstract LBA46). While chemotherapy agents with or without checkpoint inhibitors and tyrosine kinase inhibitors (TKIs) are currently utilized, none are specific to exon 20 mutations, and historical response rates from mostly small uncontrolled studies vary widely from about 6.9% to 35%, with median progression-free survival (PFS) ranging from 3 to 7 months.

Dr. Cornelissen presented preliminary safety and efficacy data from the phase 2 ZENITH20, a seven-cohort global clinical trial, specifically from cohort 4 (daily dosing) which included 48 HER2 exon 20 insertion NSCLC patients (median age, 60.5 years; women/men, 26/22) treated first-line with oral daily poziotinib (16 mg) with an Eastern Cooperative Oncology Group performance status of 1 (65%).The primary endpoint was objective response rate evaluated centrally by an independent image review committee using RECIST 1.1 criteria.

All patients have experienced treatment-related adverse events (TRAEs) with 10% considered serious, and permanent discontinuation in 13%. About 83% of patients had dose interruptions and 76% had dose reductions. The most common adverse events were diarrhea, rash, stomatitis/mucosal inflammation, and paronychia. Pneumonitis occurred in two patients (4%), with one grade 3 (2%). No grade 4/5 TRAEs were reported.

Discontinuations in 44 patients (92%), Dr. Cornelissen said, are attributed to death (5/10%), disease progression (30/63%), adverse events (1/2%), and other (8/17%), with treatment ongoing in 4 patients (8%).

The rate for the primary endpoint of objective response rate (ORR) was 43.8% (n = 21) (95% confidence interval, 29.5%-58.8%).Tumor reductions have been observed in 42/48 patients (88%) with a median reduction of 35%. One complete response was reported (2.1%), with partial responses in 20 (41.7%), stable disease in 15 (31.3%), progressive disease in 7 (14.6%), and 5 (10.4%) not evaluable. The disease control rate was 75.0%.

Dr. Cornelissen concluded: "Poziotinib shows clinically meaningful efficacy for treatment-naive NSCLC HER2 exon 20 mutations with [daily] dosing." The toxicity profile, he added, is manageable and in line with previous poziotinib studies and other second-generation EGFR TKIs.

Noting that improved tolerability and antitumor activity have been observed in the cohort 5 (8 mg b.i.d.) interim analysis, Dr. Cornelissen said that cohort 4 is ongoing with patients enrolling at 8-mg b.i.d. dosing.

HER2 mutations represents 1.7%-2.2% of NSCLC, with high-sequence homology with EGFR mutation, observed ESMO-appointed discussant Daniel S.W. Tan, PhD, National Cancer Center in Singapore. He pointed out that, while HER2 antibody drug conjugates and TKIs have gained approval in other cancer types (e.g., breast, gastric), currently no HER2 therapies are approved in NSCLC. Reviewing ZENITH20 findings (risk ratio, 43.8%; durarion of response (DoR), 5.4 months; PFS, 5.6 months), Dr. Tan stated that poziotinib is an active agent in HER2 mutated NSCLC. "One concern that remains for me is the safety profile that will require further evaluation in order to determine optimal dosing," he said.

The study was funded by Spectrum Pharmaceuticals. Other authors associated with the research disclosed full- or part-time employment with Spectrum.

COVID-19 pill // *continued from page 1*

50% in those with mild to moderate COVID-19.

When the results were found to be so favorable, the study was halted at the recommendation of an independent data-monitoring committee and in consultation with the FDA.

That initial enthusiasm is now tempered with some perspective on the pros and cons. "This anticipated drug has gotten a little more hype than it deserves," said William Schaffner, MD, professor of preventive medicine and infectious disease specialist at Vanderbilt University Medical Center in Nashville, Tenn. He and others suggest a reality check.

"It's not exactly a home run, like penicillin for strep throat," agreed Carl Fichtenbaum, MD, professor of infectious diseases at the University of Cincinnati, who is investigating a similar pill for a rival company, Atea, partnering with Roche.

Dr. Shaffner

"But it is encouraging," he said. "It will probably be an incremental improvement on what we have." The fact that it can be taken at home is a plus.

"The data show in this higher risk group [those who were studied had at least one risk factor for severe COVID-19, such as age or a medical condition], it reduces the risk of advancing to severe disease by 50%," Dr. Schaffner said. While that's a clear benefit for half, it of course leaves the other half without benefit, he said.

Others critiqued the predicted cost of the drug. The U.S. government has already agreed to pay about $700 per patient, according to a new report from Harvard T. H. Chan School of Public Health, Boston, and King's College Hospital, London. That analysis concluded that the actual cost of production for the 5-day course is $17.74.

"We fully expect that having an oral treatment that reduces the risk of hospitalizations will be significantly cost effective for society," Melissa Moody, a Merck spokesperson, told this news organization.

Merck expects to produce 10 million courses of treatment by the end of the year, with additional doses expected to be produced in 2022, according to a company press release. Earlier in 2021, Merck finalized its agreement with the U.S. government to supply about 1.7 million courses of the drug at the $700 price, once an EUA or FDA approval is given.

Study details

Details about the study findings came from a Merck press release. In the planned interim analysis, Merck and Ridgeback evaluated data from 775 patients initially enrolled in the phase 3 MOVe-OUT trial.

All adults had lab-confirmed mild to moderate COVID-19, and reported onset of symptoms within 5 days of being randomly assigned to the drug or placebo. All had at least one risk factor linked with poor disease outcome (such as older age or obesity).

The drug is a ribonucleoside and works by creating mutations in the virus's genome, halting the ability of the virus to replicate.

Through day 29 of the study, the drug reduced the risk of hospitalization or death by about 50%. While 7.3% of those who received the drug either died or were hospitalized by day 29, 14.1% of those on placebo did, a statistically significant difference ($P = .0012$).

Side effects were similar in both groups, with 35% of the drug-treated and 40% of the placebo group reporting some side effect, Merck reported.

Pros, cons, and unknowns

The ability to take the drug orally, and at home, is a definite plus, Dr. Schaffner said, compared with the monoclonal antibody treatment currently approved that must be given intravenously or subcutaneously and in certain locations.

The regimen for molnupiravir is four pills, two times daily, for 5 days, even if symptoms are mild.

The 50% reduction is not as effective as the benefit often quoted for monoclonal antibody treatment. In clinical trials of Regeneron's monoclonal antibody treatment, the regimen reduced COVID-19–related hospitalization or death in high-risk patients by 70%.

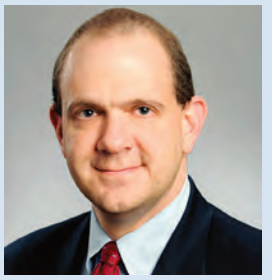
Even so, the new pill could change the pandemic's course, others say. "I think molnupiravir has the potential to change how we take care of people who have COVID and risk factors for developing severe disease," said Rajesh Tim Gandhi, MD, an infectious disease physician at Harvard Medical School in Boston.

"What we'll need to do, however, is make sure that people get tested quickly after they develop symptoms and, if they're confirmed to have

Continued on following page

***CHEST PHYSICIAN* IS ONLINE**

CHEST Physician is available at chestphysician.org.



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

CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

E-mail: chestphysiciannews@chestnet.org

CHEST Physician, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for **CHEST Physician** is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.

POSTMASTER: Send change of address (with old mailing label) to CHEST Physician, Subscription Services, 10255 W Higgins Road, Suite 280, Rosemont, IL 60018-9914.

RECIPIENT: To change your address, contact Subscription Services at 1-800-430-5450. For paid subscriptions, single issue purchases, and missing issue claims, call Customer Service at 1-833-836-2705 or e-mail custsvc.chph@fulcoinc.com

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

EDITORIAL OFFICES 2275 Research Blvd, Suite 400, Rockville, MD 20850, 973-206-3434, fax 240-221-2548

ADVERTISING OFFICES 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609
973-206-3434, fax 973-206-9378

FRONTLINE MEDICAL COMMUNICATIONS

Frontline Medical Communications Society Partners

EXECUTIVE EDITOR Kathy Scarbeck, MA
EDITOR Mark S. Lesney, PhD
CREATIVE DIRECTOR Louise A. Koenig

DIRECTOR, PRODUCTION/MANUFACTURING
Rebecca Slebodnik

DIRECTOR, BUSINESS DEVELOPMENT
Monique Michowski,
973-206-8015, cell 732-278-4549,
mmichowski@mdedge.com

RECRUITMENT SALES REPRESENTATIVE
Linda Wilson 973-290-8243,
lwilson@mdedge.com
SENIOR DIRECTOR OF RECRUITMENT SALES
Tim LaPella, 484-921-5001,
tlapella@mdedge.com

FRONTLINE
MEDICAL COMMUNICATIONS

Corporate
VP, SALES Mike Guire
VP, MEMBER MARKETING & DIGITAL PRODUCTION Amy Pfeiffer
PRESIDENT, CUSTOM SOLUTIONS JoAnn Wahl
CIRCULATION DIRECTOR Jared Sonners
DIRECTOR, CUSTOM PROGRAMS Patrick Finnegan

VICE PRESIDENT, PROPRIETARY CONFERENCES, MEDSCAPELIVE David J. Small, MBA

Cancer treatment combo // *continued from page 1*

alone. Patients in the durvalumab arms received four cycles of treatment followed by maintenance durvalumab, and those in the EP-only arm received up to six cycles of EP.

Primary outcomes data from the trial showed a significant overall survival benefit with durvalumab and EP versus EP alone (hazard ratio, 0.73), as did a subsequent analysis after a median follow-up of 25.1 months (HR, 0.75).

At median follow-up of 39.4 months, the durvalumab and EP combination showed sustained improvement in overall survival versus EP alone (HR, 0.71).

Median overall survival was 12.9 versus 10.5 months. OS was 22.9% versus 13.9% at 24 months, and 17.6% versus 5.8% at 36 months with durvalumab with EP versus EP, respectively, Dr. Paz-Ares said.

Durvalumab plus tremelimumab plus EP continued to numerically improve overall survival, compared with EP alone (HR, 0.81) Serious adverse events occurred in 32.5%, 47.4%, and 36.5% of patients in the durvalumab with EP, durvalumab plus tremelimumab plus EP, and EP arms, respectively.

The findings are "really encouraging and unprecedented, frankly," said session chair Alfredo Addeo, MD, of University Hospital, Geneva.

"They are setting the bar for competitors," he said, referencing the IMpower 133 trial looking at atezolizumab with chemotherapy in ES-SCLC.

The CASPIAN study was funded by AstraZeneca. Dr. Paz-Ares reported relationships with multiple pharmaceutical companies.

Continued from previous page

COVID, start on the pills within 5 days of developing symptoms," he said, while warning that more data are needed about the drug and the trial results.

Another concern is that the promise of a pill will stall vaccination rates, with some people figuring why get vaccinated when they can obtain the pill if they do get sick.

Relying on treatment alone won't work, Dr. Schaffner said. "Let's [also] focus on prevention, which is the vaccine. We have to keep working both sides of the street."

Dr. Gandhi added: "It's important to remember that even though molnupiravir reduced the likelihood of hospitalization and death, a number of people who received the drug still got sick enough to end up in the hospital." Also unknown, he said, is how severe their disease was and if they will develop long COVID.

The Merck study included only unvaccinated people. Might it work for those vaccinated people who get a breakthrough infection?

"From a purely scientific perspective, there is no reason to believe molnupiravir would not work in people who are vaccinated, but the overall efficacy on top of the vaccine is likely dependent on how well they were able to mount a protective immune response to the vaccine," Ms. Moody said.

As for the expected cost, Ms. Moody said that the company takes into account a number of factors in setting pricing, "but fundamentally we look at the impact of the disease, the benefits that the drug delivers to patients and to society, and at supporting ongoing drug development."

On Merck's heels

Pfizer is studying an antiviral pill, PF-07321332, a protease inhibitor that blocks the protease enzymes and halts replication of the virus.

In addition to studying the drug in infected patients at high risk of severe illness and in those at typical risk, Pfizer launched a phase 2-3 study in late September that will enroll people who live in the same household as a person with a confirmed, symptomatic COVID-19 infection to see if the drug can prevent disease in those who have been exposed.

Atea and Roche's COVID pill, AT527, is in phase 3 trials as well. AT527 is an inhibitor of polymerase, an enzyme many viruses have, to stop replications. Atea is evaluating the drug to reduce disease "burden" and for both pre- and postexposure prevention.

Role of COVID-19 pills

It may be necessary to target the coronavirus with more than one antiviral agent, said Dr. Fichtenbaum, a principal investigator for the AT527 trials.

"Sometimes viruses require two or three active agents to control their replication," he said, citing information gleaned from other viral research, such as HIV. For control of HIV infection, a cocktail or combination of antivirals is often recommended.

That may well be the case for COVID-19, Dr. Fichtenbaum said. The goal would be to attack the virus at more than one pathway.

D-dimer unreliable for ruling out pulmonary embolism in COVID-19

BY FRAN LOWRY

The plasma D-dimer assay has been used, along with clinical prediction scores, to rule out pulmonary embolism (PE) in critically ill patients for decades, but a new study suggests it may not be the right test to use in hospitalized COVID-19 patients.

The results showed that all hospitalized patients with COVID-19 and radiographic evidence of PE had plasma D-dimer levels of 0.05 mcg/mL or greater, the cutoff point for the diagnosis.

"If using D-dimer to exclude patients with PE, the increased values we found among 92.3% of patients suggest that this assay would be less useful than in the populations in which it was originally validated, among which a minority of patients had increased D-dimer values," the authors write.

"Setting higher D-dimer thresholds was associated with improved specificity at the cost of an increased false-negative rate that could be associated with an unacceptable patient safety risk," they added.

"If using D-dimer to exclude patients with PE, the increased values we found among 92.3% of patients suggest that this assay would be less useful than in the populations in which it was originally validated."

The inclusion of patients with D-dimer and computed tomography pulmonary angiography (CTPA) was necessary to estimate diagnostic performance, they note, but "this may have introduced selection bias by excluding patients unable to undergo CTPA."

"Nonetheless, given the high pretest probability of PE and low specificity observed in this and other studies, these results suggest that use of D-dimer levels to exclude PE among patients hospitalized with COVID-19 may be inappropriate and have limited clinical utility," they conclude.

Led by Constantine N. Logothetis, MD, from Morsani College of Medicine, University of South Florida, Tampa, the study was published online Oct. 8 as a Research Letter in JAMA Network Open (2021. doi: 10.1001/jamanetworkopen.2021.28802).

Uncertain utility

The authors note that the availability of D-dimer samples routinely collected from hospitalized COVID-19 patients – as well as the heterogeneity of early, smaller studies – generated uncertainty about the utility of this assay.

This uncertainty prompted them to test the diagnostic accuracy of the D-dimer assay among a sample of 1,541 patients who were hospitalized with COVID-19 at their institution between January 2020 and February 2021 for a possible PE.

They compared plasma D-dimer concentrations with CTPA, the criterion standard for diagnosing PE, in 287 of those patients.

Overall, 118 patients (41.1%) required care in the ICU, and 27 patients (9.4%) died during hospitalization.

The investigators looked at the ability of plasma D-dimer levels collected on the same day as CTPA to diagnose PE.

Thirty-seven patients (12.9%) had radiographic evidence of PE, and 250 patients (87.1%) did not.

Overall, the vast majority of patients (92.3%; n = 265 patients) had plasma D-dimer levels of 0.05 mcg/mL or more, including all patients with PE and 225 of 250 patients without PE (91.2%).

The median D-dimer values were 1.0 mcg/mL for 250 patients without PE and 6.1 mcg/mL for 37 patients with PE.

D-dimer values ranged from 0.2 mcg/mL to 128 mcg/mL among patients without PE, and from 0.5 mcg/mL to more than 10,000 mcg/mL among patients with PE. Patients without PE had statistically significantly decreased mean D-dimer values (8.7 mcg/mL vs. 1.2 mcg/mL; $P < .001$).

A D-dimer concentration of 0.05 mcg/mL was associated with a sensitivity of 100%, specificity of 8.8%, negative predictive value (NPV) of 100%, positive predictive value (PPV) of 13.9%, and a negative likelihood ratio (NLR) of less than 0.1.

The age-adjusted threshold was associated with a sensitivity of 94.6%, specificity of 22.8%, NPV of 96.6%, PPV of 13.9%, and NLR of 0.24.

The authors note that all hospitalized patients with COVID-19 and radiographic evidence of PE had plasma D-dimer levels of 0.05 mcg/mL or greater.

D-dimer in VTE may not extrapolate to COVID-19

"The D-dimer test, which is a measure of circulating byproducts of blood clot dissolution, has long been incorporated into diagnostic algorithms for venous thromboembolic [VTE] disease, including deep vein thrombosis and pulmonary embolism.

"It is uncertain whether this diagnostic use of D-dimer testing can be extrapolated to the context of COVID-19 – an illness we now understand to be associated itself with intravascular thrombosis and fibrinolysis," Matthew Tomey, MD, a cardiologist at Mount Sinai Morningside, New York, said in an interview.

"The authors of this study sought to evaluate the test characteristics of the D-dimer assay for diagnosis of pulmonary embolism in a consecutive series of 287 hospitalized patients with COVID-19 who underwent computed tomography pulmonary angiography (CTPA).

"This was a selected group of patients representing less than 20% of the 1,541 patients screened. Exclusion of data on the more than 80% of screened patients who did not undergo CTPA is a significant limitation of the study," Dr. Tomey said.

"In the highly selected, small cohort studied, representing a group of patients at high pretest probability of pulmonary embolism, there was no patient with pulmonary embolism who had a D-dimer value less than 0.5 mcg/mL.

"Yet broad ranges of D-dimer values were observed in COVID-19 patients with (0.5 to >10,000 mcg/mL) and without (0.2 to 128 mcg/mL) pulmonary embolism," he added.

Based on the presented data, it is likely true that very low levels of D-dimer decrease the likelihood of finding a pulmonary embolus on a CTPA, if it is performed, Dr. Tomey noted.

"Yet the data confirm that a wide range of D-dimer values can be observed in COVID-19 patients with or without pulmonary embolism. It is not clear at this time that D-dimer levels should be used as gatekeepers to diagnostic imaging studies such as CTPA when pretest suspicion of pulmonary embolism is high," according to Dr. Tomey.

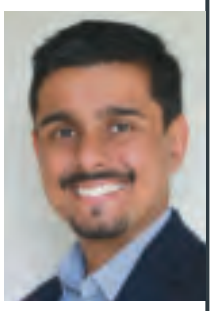
"This issue becomes relevant as we consider evolving data on use of anticoagulation in treatment of hospitalized patients with COVID-19. We learned this year that, in critically ill patients hospitalized with COVID-19, routine therapeutic anticoagulation (with heparin) was not beneficial and potentially harmful when compared with usual thromboprophylaxis," he concluded.

"As we strive to balance competing risks of bleeding and thrombosis, accurate diagnosis of pulmonary embolism is important to guide decision-making about therapeutic anticoagulation, including in COVID-19."

Dr. Logothetis and Dr. Tomey disclosed that they had no relevant financial relationships.

VIEW ON THE NEWS

Sachin Gupta, MD, FCCP, comments: As I recall from a project I was involved in during internal medicine residency, applying a Bayesian approach to PE diagnosis truly begins with a clear understanding of the pretest probability of VTE. Retrospective studies are challenging in that we do not know the pretest clinical probability of PE in these cases. That the D-dimer is unreliable in ruling in PE in the setting of infection is not entirely surprising, based on how the D-dimer was designed to be used. The results of this study should remind us of the importance of strongly considering clinical probability before testing for VTE.



> waiting for answers

COMMENTARY

Revised sarcoidosis treatment guidelines offer important updates

BY AARON B. HOLLEY, MD

Nothing about sarcoidosis is easy. In the United States, lifetime risk is 2.4% and 0.85% for African American persons and White persons, respectively. Despite study of its genetics and immunopathology, we don't know its cause. Diagnosis is challenging because noncaseating granulomas, the tissue finding associated with sarcoidosis, aren't specific for the disease. With the exception of Löfgren syndrome, a well-described sarcoid presentation that portends an excellent prognosis, initial signs and symptoms are variable and disease course is unpredictable. Alas, because sarcoid affects the lungs in more than 90% of patients, the general pulmonologist is left carrying the bag as the "sarcoidologist."

Within the past 18 months, the ATS and ERS have delivered updated guidelines for diagnosis and treatment. Predictably, neither document issues earth-shattering conclusions.

The inherent heterogeneity of sarcoid makes it challenging to study. The American Thoracic Society (ATS) is one of just a few, premier organizations that creates respiratory medicine guidelines. In 1999, they published a sarcoid consensus statement with the European Respiratory Society (ERS), another outstanding and influential respiratory medicine organization, and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG). For the past 20 years, I've been referring trainees to this document for guidance on managing their patients with sarcoid.

Twenty years later, sarcoid remains frustrating and mysterious, but much has changed. Our methods for evaluating evidence and creating guidelines are now based on the GRADE criteria. Now that we have easy access to advanced technologies such as endobronchial ultrasound, obtaining tissue for diagnosis is easier. Our study of sarcoid itself has advanced, with large cohorts providing data on phenotyping, new immunosuppressants being used for treatment, and an improved understanding of cardiac sarcoidosis. In short, we're in need of a sarcoidosis guideline for the 21st century.

Within the past 18 months, the ATS and ERS have delivered updated guidelines for diagnosis and treatment. Despite the advancements cited above, sarcoid remains difficult to study. So predictably, neither document issues earth-shattering conclusions. Truth be told, well-done guidelines rarely do. They do provide several important updates that physicians managing patients with sarcoid should note.

The guideline on diagnosis provides recommendations for routine monitoring after diagnosis. Many practicing clinicians took from the 1999 ATS/ERS/WASOG consensus statement that all patients with sarcoid needed to be seen annually. At pulmonary clinics where I've worked, we've defaulted to annual follow-up for everyone, usually with chest radiography, lab testing, electrocardiography, and referral to ophthalmology. Because a majority of patients with sarcoid will remain asymptomatic or experience spontaneous remission, this practice never really seemed cost effective or clinically efficient. The new guidelines are far more proscriptive on what monitoring is required and grade requirements at specific levels of certainty and often advise symptom-based assessments in lieu of reflexive annual testing.

The ERS guideline on treatment provides a thoughtful discussion of corticosteroid indications and dosing, broken down by underlying disease severity (assessed by lung function abnormalities and imaging). It also recognizes that two of the most common sarcoid symptoms are fatigue and dyspnea, which are both inherently nonspecific. In practice, proving these symptoms are directly attributable to sarcoid is challenging. The treatment guideline allows for flexibility in these cases, with shared decision-making and trials of low-dose steroids recommended. This seems an excellent hedge against overtreatment with immunosuppressive medications that have harmful side effects.

The ATS and ERS guidelines are not without controversy. Their approach to cardiac sarcoid differs slightly from that recommended by a commonly cited Heart Rhythm Society consensus statement, and despite discussing treatment options, the section on fatigue is quite limited. These two facts and other limitations largely reflect differing interpretations of the limited data; they do not detract from the overall importance of the ATS and ERS guidelines. Sarcoid remains an enigma, but little by little the academic physicians at the ATS and ERS are providing clarity.

Dr. Holley is program director, pulmonary and critical care medical fellowship, department of medicine, Walter Reed National Military Medical Center, Bethesda, Maryland. He has received a research grant from Fisher-Paykel and income from the American College of Chest Physicians.

Sachin Gupta, MD, FCCP, comments: In my observation, community and academic center practices alike tend to have wide variation in how patients with sarcoidosis are managed and this may be in part due to the large time-gap since the large society guidelines have been updated. Inequities in care may arise as a result. Both the ATS guideline recommendations on diagnosis and the ERS guidelines for treatment of sarcoidosis are must reads for those of us who regularly see patients with sarcoidosis. Though mostly leaning on consensus opinion because of a lack of published data, these recommendations are driven by leading researchers in the field and should help raise the level of care of patients with this disease.

LUNG CANCER

COVID especially dangerous for those with mesothelioma

BY M. ALEXANDER OTTO

MDedge News

Clinicians should pay particular attention to malignant pleural mesothelioma patients with COVID-19. Among people with thoracic malignancies, they have an especially high risk of bad outcomes, according to Susana Cedres, MD, PhD, a thoracic medical oncologist at Vall d'Hebron University Hospital, Barcelona.

At the annual World Conference on Lung Cancer, she reported on her institution's experience during the first year of the pandemic before widespread vaccine rollouts. Among 38 malignant pleural mesothelioma (MPM) patients, 7 (18%) patients were diagnosed with COVID-19 and of these, 3 patients were asymptomatic, 4 (57%) died of complications including bilateral pneumonia within a median of less than half a month after diagnosis, and a 5th patient died from MPM progression.

The findings confirm the particular risk of COVID in MPM. According to researchers reporting in Scientific Reports (2021 Feb 4. doi: 10.1038/s41598-021-82384-0), mesothelioma was the only cancer linked to significantly worse outcomes. Other risks included tuberculosis, drug use, hepatitis, HIV/AIDS, cardiomyopathy, and diabetes.

"There really is a need for more inclusion of MPM patients in international [COVID] registries" to better characterize the course of infection and improve outcomes, said study discussant Francoise Galateau-Salle, MD, PhD, of the Cancer Center Leon Berard in Lyon, France. Among the seven positive cases in Barcelona, almost all had comorbidities, with the most common being cardiovascular disease in four patients (57%).

Dr. Cedres is an adviser and/or reported travel expenses from a number of companies, including Merck, Pfizer, and Bristol-Myers Squibb. Dr. Galateau-Salle had no disclosures.

> an incomplete
> echo

Cardiogenic shock teams again tied to lower mortality

BY PATRICE WENDLING

A large multicenter study provides further evidence supporting the rationale for multidisciplinary teams for cardiogenic shock, one of the most lethal diseases in cardiovascular medicine.

The analysis of 24 critical care ICUs in the Critical Care Cardiology Trials Network showed that the presence of a shock team was independently associated with a 28% lower risk for CICU mortality (23% vs. 29%; odds ratio, 0.72; $P = .016$).

Patients treated by a shock team also had significantly shorter CICU stays and less need for mechanical ventilation or renal replacement therapy, as reported in the Journal of the American College of Cardiology (2021 Sep;78[13]:1309-17).

THINKSTOCK

"It's observational, but the association that we're seeing here, just because of our sample size, is the strongest that's been published yet," lead author Alexander Papolos, MD, MedStar Washington Hospital Center, said in an interview.

Although a causal relationship cannot be drawn, the authors suggest several factors that could explain the findings, including a shock team's ability to rapidly diagnose and treat cardiogenic shock before multiorgan dysfunction occurs.

Centers with shock teams also used significantly more pulmonary artery catheters (60% vs. 49%; adjusted OR, 1.86; $P < .001$) and placed them earlier (0.3 vs. 0.66 days; $P = .019$).

Pulmonary artery catheter (PAC) use has declined after earlier trials like ESCAPE showed little or no benefit in other acutely ill patient groups, but positive results have been reported recently in cardiogenic shock, where a PAC is needed to determine the severity of the lesion and the phenotype, Dr. Papolos observed.

A 2018 study showed PAC use was tied to increased survival among patients with acute myocardial infarction cardiogenic shock (AMI-CS) supported with the Impella (Abiomed) device (Am Heart J. 2018 Aug;202:33-8). Additionally, a 2021 study by the Cardiogenic Shock Working Group demonstrated a dose-dependent survival response based on the completeness of hemodynamic assessment by PAC prior to initiating mechanical circulatory support (MCS).

A third factor might be that a structured, team-based evaluation can facilitate timely and optimal MCS device selection, deployment, and management, suggested Dr. Papolos.

Centers with shock teams used more advanced types of MCS – defined as Impella, TandemHeart (LivaNova), extracorporeal membrane oxygenation, and temporary or durable surgical ventricular assist devices – than those without a shock team (53% vs. 43%; adjusted OR, 1.73; $P = .005$) and did so more often as the initial device (42% vs. 28%; $P = .002$).

Overall MCS use was lower at shock team centers (35% vs. 43%), driven by less frequent use of intra-aortic balloon pumps (58% vs. 72%).

"The standard, basic MCS has always been the balloon pump because it's something that's easy to put in at the cath lab or at the bedside," Dr. Papolos said.

"So, if you take away having all of the information and having the right people at the table to discuss what the best level of support is, then you're going to end up with balloon pumps, and that's what we saw here."

The study involved 6,872 consecutive medical admissions at 24 level 1 CICU centers during an annual 2-month period from 2017 to 2019. Of these, 1,242 admissions were for cardiogenic shock and 546 (44%) were treated at 1 of 10 centers with a shock team.

Shock team centers had higher-acuity patients than centers without a shock team (Sequential Organ Failure Assessment score, 4 vs. 3) but a similar proportion of patients with AMI-CS (27% vs. 28%).

Among all admissions, CICU mortality was not significantly different between centers with and without a shock team.

For cardiogenic shock patients treated at centers with and without a shock team, the median CICU stay was 4.0 and 5.1 days, respectively, mechanical ventilation was used in 41% and 52%, respectively, and new renal replacement therapy in 11% and 19%, respectively ($P < .001$ for all).

Shock team centers used significantly more PACs for AMI-CS and non–AMI-CS admissions; advanced MCS therapy was also greater in the AMI-CS subgroup.

Lower CICU mortality at shock team centers persisted among patients with non-AMI-CS (adjusted OR, 0.67; $P = .017$) and AMI-CS (adjusted OR, 0.79; $P = .344$).

"This analysis supports that all AHA level 1 cardiac ICUs should strongly consider having a shock team," Dr. Papolos said.

Evidence from single centers and the National Cardiogenic Shock Initiative has shown improved survival with a cardiogenic shock algorithm (J Am Coll Cardiol. 2019 Apr;73[13]:1659-69), but this is the first report specifically comparing no shock teams with shock teams, Perwaiz Meraj, MD, Northwell Health, Manhansett, N.Y., told this news organization.

"People may say that it's just another paper that's saying, 'shock teams, shock teams, rah, rah, rah,' but it's important for all of us to really take a close look under the covers and see how are we best managing these patients, what teams are we putting together, and to create systems of care, where if you're at a center that really doesn't have the capabilities of doing this, then you should partner up with a center that does," he said.

Notably, the 10 shock teams were present only in medium or large urban, academic medical centers with more than 500 beds. Although they followed individual protocols, survey results show service-line representation, structure, and operations were similar across centers.

They all had a centralized way to activate the shock team, the service was 24/7, and members came from areas such as critical care cardiology (100%), cardiac surgery (100%), interventional cardiology (90%), advanced heart failure (80%), and extracorporeal membrane oxygenation service (70%).

Limitations of the study include the possibility of residual confounding, the fact that the registry did not capture patients with cardiogenic shock managed outside the CICU or the time of onset of cardiogenic shock, and data were limited on inotropic strategies, sedation practices, and ventilator management, the authors wrote.

"Although many critics will continue to discuss the lack of randomized controlled trials in cardiogenic shock, this paper supports the process previously outlined of a multidisciplinary team–based approach improving survival," Dr. Meraj and William W. O'Neill, MD, director of the Center for Structural Heart Disease and Henry Ford Health System, Detroit, and the force behind the National Cardiogenic Shock Initiative, wrote in an accompanying editorial (J Am Coll Cardiol. 2021 Sep;78[13]:1318-20).

They point out that the report doesn't address the escalation of care based on invasive hemodynamics in the CICU and the protocols to prevent acute vascular/limb complications (ALI) that can arise from the use of MCS.

"Many procedural techniques and novel CICU models exist to mitigate the risk of ALI in CS patients with MCS," they wrote. "Finally, escalation of care and support is vital to the continued success of any shock team and center."

One coauthor has served as a consultant to Abbott. Another has served as a consultant to the Abiomed critical care advisory board. All other authors reported having no relevant financial relationships.

Dr. Meraj has received research and grant funding from Abiomed, Medtronic, CSI, and Boston Scientific. Dr. O'Neill has received consulting/speaker honoraria from Abiomed, Boston Scientific, and Abbott.

LARGE CART-BENCHMARKED IMAGING

AI-CORE LAB VALIDATED ALGORITHMS*

A VALUE GREATER THAN YOU'D EXPECT

KOSMOS
by EchoNous

> the status quo

Kosmos ultraportable ultrasound saves time at bedside and reduces echo referrals by greater than 90%.

- **CW/PW Doppler** benchmarked against cart-based systems
- AI-fueled Core Lab validated algorithms for systolic function*
- Proprietary xM chip gives you the power of 64/128 channels in a handheld

xM 64 128

*With Us2.AI — AI driven echo analysis

See how Us2.ai and Kosmos are changing the way physicians practice medicine @ kosmosplatform.com

Pandemic adds more weight to the increasing burden of obesity in children

BY KATE JOHNSON
MDedge News

American children gained a lot of weight in the last year, setting a dangerous trajectory toward metabolic disease that requires urgent policy change, according to a new report from the Robert Wood Johnson Foundation.

"Our nation's safety net is fragile, outdated, and out of reach for millions of eligible kids and caregivers," said Jamie Bussel, senior program officer at the RWJF, and senior author of the report. She added that the pandemic further fractured an already broken system that disproportionately overlooks "children of color and those who live farthest from economic opportunity."

Think 'bigger and better'

Ms. Bussel said, during a press conference, that congress responded to the pandemic with "an array of policy solutions," but it's now time to think "bigger and better."

"There have been huge flexibilities deployed across the safety net program and these have been really important reliefs, but the fact is many of them are temporary emergency relief measures," she explained.

For the past 3 years, the RWJF's annual State of Childhood Obesity report has drawn national and state obesity data from large surveys including the National Survey of Children's Health, the Youth Risk Behavior Surveillance System, the WIC Participant and Program Characteristics Survey, and the National Health and Nutrition Examination Survey.

Similar to in past years, this year's data show that rates of obesity and overweight have remained relatively steady and have been highest among minority and low-income populations. For example, data from the 2019-2020 National Survey of Children's Health, along with an analysis conducted by the Health Resources and Services Administration's Maternal and Child Health Bureau, show that one in six – or 16.2% – of youth aged 10-17 years have obesity.

VIEW ON THE NEWS

Mary Cataletto, MD, FCCP, comments: As children return to school, overweight and obesity are major concerns. Obesity is a significant risk factor for obstructive breathing disorders from snoring to apnea and has been associated with daytime symptoms of poor memory and focus, which impact learning. This is further compounded by recent supply chain issues and labor shortages that impact the quality and availability of nutritious options in school lunch programs. Substituting or supplementing with fast foods (which are generally high calorie) brought from home or purchased outside of school can further increase the obesity epidemic.

While non-Hispanic Asian children had the lowest obesity rate (8.1%), followed by non-Hispanic White children (12.1%), rates were significantly higher for Hispanic (21.4%), non-Hispanic Black (23.8%), and non-Hispanic American Indian/Alaska Native (28.7%) children, according to the report.

"Additional years of data are needed to assess whether obesity rates changed after the onset of the pandemic," explained Ms. Bussel.

Digging deeper

Other studies included in this year's report were specifically designed to measure the impact of the pandemic, and show a distinct rise in overweight and obesity, especially in younger children. For example, a retrospective cohort study using data from Kaiser Permanente Southern California (JAMA. 2021;326[14]:1434-6) showed the rate of overweight and obesity in children aged 5-11 years rose to 45.7% between March 2020 and January 2021, up from 36.2% before the pandemic.

Another of these studies, which was based on national electronic health records of more than 430,000 children, showed the obesity rate crept from 19.3% to 22.4% between August 2019 and August 2020 (Morb Mortal Wkly Rep. 2021;70:1278-83).

"The lid we had been trying desperately to put on the obesity epidemic has come off again," said Sandra G. Hassink, MD, MSc, who is medical director of the American Academy of Pediatrics Institute for Healthy Childhood Weight.

"In the absence of COVID we had been seeing slow upticks in the numbers – and in some groups we'd been thinking maybe we were headed toward stabilization – but these numbers blow that out of the water ... COVID has escalated the rates," she said in an interview.

"Unfortunately, these two crises – the COVID pandemic, the childhood obesity epidemic – in so many ways have exacerbated one another," said Ms. Bussel. "It's not a huge surprise that we're seeing an increase in childhood obesity rates given the complete and utter disruption of every single system that circumscribes our lives."

The systems that feed obesity

Addressing childhood obesity requires targeting far beyond healthy eating and physical activity, Ms. Bussel said.

"As important is whether that child has a safe place to call home.

Addressing childhood obesity requires targeting far beyond healthy eating.

MS. BUSSEL

Does mom or dad or their care provider have a stable income? Is there reliable transportation? Is their access to health insurance? Is there access to high-quality health care? ... All of those factors influence the child and the family's opportunities to live well, be healthy, and be at a healthy weight," she said.

The report includes a list of five main policy recommendations.

- Making free, universal school meal programs permanent.
- Extending eligibility for WIC, the Special Supplemental Nutrition Program for Women, Infants, and

Children, to postpartum mothers and to children through age 6.
- Extending and expanding other programs, such as the Child Tax Credit.
- Closing the Medicaid coverage gap.
- Developing a consistent approach to collecting obesity data organized by race, ethnicity, and income level.

"Collectively, over at least the course of the last generation or two, our policy approach to obesity prevention has not been sufficient. But that doesn't mean all of our policy approaches have been failures," Ms. Bussel said during an interview.

"Policy change does not always need to be dramatic to have a real impact on families."

"In the absence of COVID we had been seeing slow upticks in the numbers – and in some groups we'd been thinking maybe we were headed toward stabilization – but these numbers blow that out of the water."

Fighting complacency

For Dr. Hassink, one of the barriers to change is society's level of acceptance. She said an identifiable explanation for pandemic weight gain doesn't mean society should simply shrug it off.

"If we regarded childhood obesity as the population level catastrophe that it is for chronic disease maybe people would be activated around these policy changes," she said.

"We're accepting a disease process that wreaks havoc on people," noted Dr. Hassink, who was not involved in the new report.

"I think it's hard for people to realize the magnitude of the disease burden that we're seeing. If you're in a weight-management clinic or any pediatrician's office you would see it – you would see kids coming in with liver disease, 9-year-olds on [continuous positive airway pressure] for sleep apnea, kids needing their hips pinned because they had a hip fracture because of obesity.

"So, those of us that see the disease burden see what's behind those numbers. The sadness of what we're talking about is we know a lot about what could push the dial and help reduce this epidemic and we're not doing what we already know," added Dr. Hassink.

Ms. Bussel and Dr. Hassink reported that they had no conflicts.

KALI9/E+/GETTY IMAGES/BLURRED

Age, C-reactive protein linked to death risk in diabetes

BY MIRIAM E. TUCKER

Both high C-reactive protein (CRP) and older age predict mortality from COVID-19 in patients with diabetes, according to data from the retrospective ACCREDIT cohort study, presented at the virtual annual meeting of the European Association for the Study of Diabetes (EASD 2021) by Daniel Kevin Llanera, MD, of the Imperial College, London.

The combination of older age and high levels of the inflammatory marker CRP were linked to a tripled risk for death by day 7 after hospitalization for COVID-19 among people with diabetes. But, in contrast to other studies, recent A1c and body mass index did not predict COVID-19 outcomes.

The study, conducted involved 1,004 patients with diabetes admitted

with COVID-19 to seven hospitals in northwest England from Jan. 1 through June 30, 2020. The patients were a mean age of 74.1 years, 60.7% were male, and 45% were in the most deprived quintile based on the U.K. government deprivation index.

The primary outcome, death within 7 days of admission, occurred in 24%. By day 30, 33% had died.

These rates are higher than the rate found in previous studies, possibly because of greater socioeconomic deprivation and older age of the population, Dr. Llanera speculated.

A total of 7.5% of patients received intensive care by day 7 and 9.8% required intravenous insulin infusions. On univariate analysis, insulin infusion was found to be protective, with those receiving it half as likely to die as those who didn't need IV insulin (odds ratio [OR], 0.5).

In contrast, chronic kidney disease in people younger than 70 years increased the risk of death more than twofold (OR, 2.74), as did type 2 diabetes compared with other diabetes types (OR, 2.52).

In multivariate analysis, CRP and age emerged as the most significant predictors of the primary outcome, with those deemed high risk by a logistic regression model having an OR of 3.44 for death by day 7 compared with those at lower risk based on the two factors.

Dr. Llanera reported having no relevant financial relationships.

SLEEP STRATEGIES

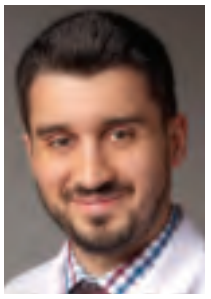
The apnea-hypopnea index: Limitations and future directions

BY WISSAM MANSOUR, MD, AND CHRISTINE H. J. WON, MD, MS

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse resulting in intermittent hypoxemia and hypercapnia, large intrathoracic pressure swings, and cortical arousals. The rate of apneas and hypopneas observed during sleep, the apnea-hypopnea index (AHI), has been used for decades to diagnose OSA and to classify its severity. Despite the wide acceptance of this metric by the sleep medicine community, clinical research has found poor correlations between the AHI- and OSA-related complications or symptoms. We have come to learn that the AHI is an oversimplification of a complex and diverse disease process. (Punjabi. *Chest*. 2016;149[1]:16-9).

The most important features of a disease metric are reliability, and the ability to predict clinically relevant outcomes. The reliability of the AHI has been in question due to substantial night-to-night variability that can lead to missed diagnosis and disease severity misclassification (Dzierzewski et al. *J Clin Sleep Med*. 2020;16[4]:539-44). Furthermore, the AHI fails to reflect some important physiologic derangements resulting from respiratory events. Apart from imperfectly set thresholds for scoring, it disregards the depth and the duration of ventilatory disturbances. For example, a hypopnea lasting 30 seconds and resulting in a decrease of 10% in oxyhemoglobin saturation is considered equivalent to a hypopnea lasting 10 seconds and resulting in a decrease of 4% in oxyhemoglobin saturation. The AHI also assumes that apneas and hypopneas are equal in their biological effects regardless of when they occur during sleep (NREM vs REM), despite reports suggesting that the sequalae of OSA are sleep-stage dependent (Varga, Mokhlesi. *Sleep Breath*. 2019;23[2]:413-23). This is further complicated by the varying hypopnea definitions and the difficulties in differentiating obstructive vs central hypopneas. It is doubtful that these events, which differ in mechanism, would result in similar outcomes.

Over the past decade, our understanding of the different pathophysiological mechanisms leading to OSA



Dr. Mansour

Dr. Won

has grown substantially, suggesting the need for a phenotype-specific treatment approach (Zinchuk, Yaggi. *Chest*. 2020;157[2]:403-20). The reliance on a single metric that does not capture this heterogeneity may prove detrimental to our therapeutic efforts. One extremely important dimension that is missed by the AHI is the patient. Individual response to airway obstruction varies with age, genetics, gender, and comorbidities, among other things. This may explain the difference in symptoms and outcomes experienced by patients with the same AHI. During the era of precision medicine, the concept of defining a clinical condition by a single test result, without regard to patient characteristics, is antiquated.

Several studies have attempted to propose complementary metrics that may better characterize OSA and predict outcomes. The hypoxic burden has gained a lot of attention as it is generally felt that hypoxemia is a major factor contributing to the pathogenesis of OSA-related comorbidities. Azarbarzin, et al. reported a hypoxic burden metric by measuring the area under the oxygen desaturation curve during a respiratory event (Azarbarzin et al. *Eur Heart J*. 2019;40[14]:1149-57). It factors the length and depth of the desaturations into a single value that expresses the average desaturation burden per hour of sleep time. The hypoxic burden was independently predictive of cardiovascular mortality in two large cohorts. Interestingly, the AHI did not have such an association. Similarly, another novel proposed parameter, the oxygen desaturation rate (ODR), outperformed the AHI in predicting cardiovascular outcomes in severe OSA patients (Wang et al. *J Clin Sleep Med*. 2020;16[7]:1055-62). The ODR measures the speed of an oxygen desaturation during an apnea event. Subjects with a faster ODR were found to have higher blood pressure values and variability. The authors hypothesized that slower desaturations generate hypoxemia-conditioning that may protect from exaggerated hemodynamic changes. These findings of novel hypoxemia metrics, albeit having their own limitations, recapitulate the need to move beyond the AHI to characterize OSA.

The apnea-hypopnea event duration is another overlooked feature that may impact OSA outcomes. Butler, et al. demonstrated that shorter event duration predicted a higher all-cause mortality over and beyond that predicted by AHI (Butler et al. *Am J Respir Crit Care Med*. 2019;199[7]:903-12). These results contrast views that early arousals in response to respiratory events may improve outcomes as they reflect a protective mechanism to prevent further hypoxemia and sympatho-excitation. For example, Ma, et al. found that higher percentage of total sleep time spent in apnea/hypopnea (AHT%) predicted worse daytime sleepiness to a higher degree than standard AHI (Ma et al. *Sci Rep*. 2021;11[1]:4702). However, shorter event duration may represent lower arousal thresholds (increased excitability), and ventilatory control instability (higher loop gain), predisposing patients to augmented sympathetic activity. Along similar lines, the intensity of respiratory-related arousals (as mea-

Continued on following page

Finding your passion in fellowship

BY KEVIN SWIATEK, DO

(This post is part of Our Life as a Fellow blog post series. This series includes "fellow life lessons" from current trainees in leadership with CHEST.)

Finding your passion in fellowship is an integral part of career development and has a profound impact on a young professional's personal satisfaction. This can be a difficult task, but it can be accomplished by finding a mentor, thinking about long-term career goals, and considering what re-energizes you.

Entering fellowship, some may have a preconceived idea of who they would like to be upon completion of training: An asthma specialist, a physician-scientist, a critical care junkie, etc. For most of us, fellowship is a black box of opportunity with endless paths and permutations. It can be difficult to navigate this landscape, as the path may meander and a few initial interests may develop into true passions.

During my fellowship, I have been fortunate to have had many great teachers and experiences caring for patients with pulmonary hypertension, my current primary focus. Here are a few steps I have taken in pursuit of finding my passion over the past several years of post-graduate medical education. ***Disclaimer: I am still a work in progress.***

First, find a mentor. For me it was easy – I remember interviewing for fellowship with my mentor and thinking: "That is who I want to be." I think this is hugely important. Use the insights, mistakes, and successes of someone you admire (from near or far) to help guide you. Initially, while getting to know my mentor,

Passion // *Continued on following page*

Continued from previous page

sured by EEG wavelet transformation) was found to be independent of preceding respiratory stimulus, with higher arousal intensity levels correlating with higher respiratory and heart rate responses (Amatoury et al. *Sleep*. 2016;39[12]:2091-100). The contribution of arousals to OSA morbidity is of particular importance for women in whom long-term outcomes of elevated AHI are poorly understood. Bearing in mind the differences in the metrics used, these results underscore the role of event duration and arousability in the pathogenesis of OSA-related morbidity.

The AHI is certainly an important piece of data that is informative and somewhat predictive. However, when used as a sole disease-defining metric, it has yielded disappointing results, especially after OSA treatment trials failed to show cardiovascular benefits despite therapies achieving a low residual AHI. As we aim to achieve a more personalized approach for diagnosing and treating OSA, we need to explore beyond the concept of a single metric to define a heterogenous and complex disorder. Instead of relying on the frequency of respiratory events, it is time to use complementary polysomnographic data that better reflect the origin and systemic effects of these disturbances. Machine-learning methods may offer sophisticated approaches to identifying polysomnographic patterns for future research. Clinical characteristics will also likely need to be considered in OSA severity scales. The identification of symptom subtypes or blood biomarkers may help identify patient groups who may be impacted differently by OSA, and consequently have a different treatment response (Malhotra et al. *Sleep*. 2021;44[7]:zsab030).

Almost half a century has lapsed since the original descriptions of OSA. Since then, our understanding of the disorder has improved greatly, with much still to be discovered, but our method of disease capture is unwavering. Future research requires a focus on novel measures aimed at identifying OSA endophenotypes, which will transform our understanding of disease traits and propel us into personalized therapies.

Dr. Mansour is Assistant Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Duke University School of Medicine, Durham, North Carolina. Dr. Won is Associate Professor of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University School of Medicine; and VA Connecticut Healthcare System, West Haven, Connecticut.

Passion // *Continued from previous page*

it was more comfortable to follow from a safe distance without making an official commitment. This was a slow process that allowed me to explore multiple clinical and research interests simultaneously.

Once your mind is set, stating your professional interests in a concise way helps you and your mentor define and differentiate hobbies from passions.

The practice of medicine is still very much an apprenticeship, so having someone to act as a sounding board remains important.

Mentorship is also critical for networking, which is important for professional growth and life beyond fellowship. Our community is small, and "people know people."

What happens if you can't find a perfect mentor? Don't worry! Try out as many mentors as you can find. You can learn from every conversation and every relationship. Sometimes the path taken is just as important as the destination.

Second, think about your 5- or 10-year plan. Ultimately, when training is over, we will graduate from fellowship and be released into the wild.

The skills we have obtained in training are going to be the foundation for the rest of our careers. Where would you like to be a few years post-training? In a lab? Private practice? Rural medicine? Teaching?

Does the energy you are spending in fellowship to develop your passion extend beyond fellowship? Part of the excitement of pursuing a passion is envisioning how it may develop over the period of coming years. I envision honing my skills as a master general pulmonary clinician and then narrowing my focus to create a pulmonary hypertension care center of excellence.

I think these are important points to consider while you have the protected headspace of fellowship to experiment and explore, and while you are not constrained by contractual obligations.

Third, think about what personally and professionally energizes you. Especially in the context of an ongoing global pandemic, burnout and physician dissatisfaction are at an all-time high. Acknowledge that your job is tough, and try to identify the things that will keep the engine running.

This sounds straightforward, but you have to decide what recharges you and acknowledge those things that don't. The importance of determining things that energize me did not occur to me until I started searching for my first job. This forced me to make a list of things that contributed to my happiness and dissatisfaction. Most future employers are skilled at asking about these qualities. A happy employee is productive and effective at his or her job!

If you are in training, take some time to get creative and answer the questions above. Doodle, make lists, or journal—find a moment to reflect on your hard work and on the promise of your future.

Dr. Swiatek is a third-year Chief Fellow in the Division of Pulmonary and Critical Care Medicine at Virginia Commonwealth University in Richmond, Virginia. Dr. Swiatek is a member of the CHEST Trainee Work Group. His clinical interests include general pulmonary medicine, care of patients with pulmonary hypertension, and using point-of-care ultrasound (POCUS) as a diagnostic tool in the medical intensive care unit. His scholarly interests include implementation of fellowship medical education, teaching POCUS, and clinical and diagnostic assessment of patients with pulmonary hypertension.

Reprinted from Thought Leader Blog. August 23, 2021. www.chestnet.org.

This month in the journal *CHEST*®

Editor's picks

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

Precision Medicine and Heterogeneity of Treatment Effect in Therapies for Acute Respiratory Distress Syndrome.
By Dr. N. Ferguson, et al.

How We Do It: Managing Cough in Idiopathic Pulmonary Fibrosis.
By Dr. J. Swigris, et al.

Executive Summary: Optimal Noninvasive Ventilation Medicare Access Promotion (ONMAP). *By Dr. P.Gay, et al.*

Screening for Lung Cancer: CHEST Guideline and Expert Panel Report – Executive Summary.
By Dr. P. J. Mazzone, et al.

Nucala
(mepolizumab)
Injection 100 mg/mL

The targeted therapy for 4 eosinophil-driven diseases

Severe eosinophilic asthma (SEA)

NOW APPROVED

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Eosinophilic granulomatosis with polyangiitis (EGPA)

Hypereosinophilic syndrome (HES)

NUCALA is for the:

- add-on maintenance treatment of patients 6+ with SEA. Not for acute bronchospasm or status asthmaticus.
- add-on maintenance treatment of CRSwNP in patients 18+ with inadequate response to nasal corticosteroids.
- treatment of adult patients with EGPA.
- treatment of patients aged 12+ with HES for ≥6 months without an identifiable non-hematologic secondary cause.

Important Safety Information

CONTRAINDICATIONS

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

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

Visit Nucala4EOS.com to learn more →

Important Safety Information (cont'd)

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

Herpes zoster infections have occurred in patients receiving NUCALA. 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.

ADVERSE REACTIONS

Most common adverse reactions (≥5%) in patients receiving NUCALA:

- Severe asthma trials: headache, injection site reaction, back pain, fatigue
- CRSwNP trial: oropharyngeal pain, arthralgia
- EGPA and HES trials (300 mg of NUCALA): no additional adverse reactions were identified to those reported in severe asthma clinical trials

Systemic reactions, including hypersensitivity, occurred in clinical trials in patients receiving NUCALA. Manifestations included rash, pruritus, headache, myalgia, flushing, urticaria, erythema, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, stridor, angioedema, and multifocal skin reaction. A majority of systemic reactions were experienced the day of dosing.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women with asthma 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.

MPLJRNA210001 August 2021
Produced in USA.

BRIEF SUMMARY

NUCALA (mepolizumab) for injection, for subcutaneous use
NUCALA (mepolizumab) injection, for subcutaneous use
The following is a brief summary only; 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 adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype *[see Use in Specific Populations (8.4) and Clinical Studies (14.1) of full prescribing information]*.

Limitations of Use

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

1.2 Maintenance Treatment of Chronic Rhinosinusitis with Nasal Polyps

NUCALA is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

1.3 Eosinophilic Granulomatosis with Polyangiitis

NUCALA is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

1.4 Hypereosinophilic Syndrome

NUCALA is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

4 CONTRAINDICATIONS

NUCALA is contraindicated in patients with a history of hypersensitivity to mepolizumab or excipients in the formulation *[see Warnings and Precautions (5.1) and Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

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

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience in Severe Asthma

Adult and Adolescent Patients Aged 12 Years and Older

A total of 1,327 patients with severe asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trial 1, NCT01000506; Trial 2, NCT01691521; and Trial 3, NCT01691508). 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 patients 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 patients had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1) of full prescribing information]*. Of the patients 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 patients received NUCALA (mepolizumab 100 mg subcutaneous) for at least 24 weeks. Serious adverse events that occurred in more than 1 patient and in a greater percentage of patients receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 patients vs. 0 patients, respectively). Approximately 2% of patients receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of patients 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 Patients with Severe Asthma (Trials 2 and 3)

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

52-Week Trial: Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in patients receiving mepolizumab 75 mg IV compared with 2 patients in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions: In Trials 1, 2, and 3 described above, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 3% in the group receiving NUCALA 100 mg and 5% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of patients in the group receiving NUCALA 100 mg and 2% of patients in the placebo group. 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 patients in the group receiving NUCALA 100 mg and 3% of patients 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 patients 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 patients receiving NUCALA 100 mg compared with 3% in patients receiving placebo.

Long-term Safety: Nine hundred ninety-eight patients received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.

Pediatric Patients Aged 6 to 11 Years

The safety data for NUCALA is based upon 1 open-label clinical trial that enrolled 36 patients with severe asthma aged 6 to 11 years. Patients received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of NUCALA administered subcutaneously once every 4 weeks. Patients received NUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 patients received NUCALA for a further 52 weeks (long phase). The adverse reaction profile for patients aged 6 to 11 years was similar to that observed in patients aged 12 years and older.

6.2 Clinical Trials Experience in Chronic Rhinosinusitis with Nasal Polyps

A total of 407 patients with CRSwNP were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received NUCALA 100 mg or placebo subcutaneously once every 4 weeks. Patients had recurrent CRSwNP with a history of prior surgery and were on nasal corticosteroids for at least 8 weeks prior to screening *[see Clinical Studies (14.2) of full prescribing information]*. Of the patients enrolled, 35% were female, 93% were White, and ages ranged from 18 to 82 years. Approximately 2% of patients receiving NUCALA 100 mg withdrew from study treatment due to adverse events compared with 2% of patients receiving placebo.

Table 2 summarizes adverse reactions that occurred in ≥3% of NUCALA-treated patients and more frequently than in patients treated with placebo in the CRSwNP trial.

Table 2. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with CRSwNP

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 206) %	Placebo (n = 201) %
Oropharyngeal pain	8	5
Arthralgia	6	2
Abdominal Pain Upper	3	2
Diarrhea	3	2
Pyrexia	3	2
Nasal dryness	3	<1
Rash	3	<1

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic [type I hypersensitivity] and other) reactions was <1% in the group receiving NUCALA 100 mg and <1% in the placebo group. Systemic allergic (type I hypersensitivity) reactions were reported by <1% of patients in the group receiving NUCALA 100 mg and no patients in the placebo group. The manifestations of systemic allergic (type I hypersensitivity) reactions included urticaria, erythema, and rash and 1 of the 3 reactions occurred on the day of dosing. Other systemic reactions were reported by no patients in the group receiving NUCALA 100 mg and <1% of patients in the placebo group.

Injection Site Reactions

Injection site reactions (e.g., erythema, pruritus) occurred at a rate of 2% in patients receiving NUCALA 100 mg compared with <1% in patients receiving placebo.

6.3 Clinical Trials Experience in Eosinophilic Granulomatosis with Polyangiitis

A total of 136 patients with EGPA were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients enrolled had a diagnosis of EGPA for at least 6 months prior to enrollment with a history of relapsing or refractory disease and were on a stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day (but not greater than 50 mg/day) for at least 4 weeks prior to enrollment *[see Clinical Studies (14.3) of full prescribing information]*. Of the patients enrolled, 59% were female, 92% were White, and ages ranged from 20 to 71 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of NUCALA and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of NUCALA and 1% of patients in the placebo group. The manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving 300 mg of NUCALA included rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor. Systemic non-allergic reactions were reported by 1 (1%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of systemic non-allergic reactions reported in the group receiving 300 mg of NUCALA was angioedema. Half of the systemic reactions in patients receiving 300 mg of NUCALA (2/4) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving 300 mg of NUCALA compared with 13% in patients receiving placebo.

6.4 Clinical Trials Experience in Hypereosinophilic Syndrome

A total of 108 adult and adolescent patients aged 12 years and older with HES were evaluated in a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients with non-hematologic secondary HES or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients must have been on a stable dose of background HES therapy for the 4 weeks prior to randomization [*see Clinical Studies (14.4) of full prescribing information*]. Of the patients enrolled, 53% were female, 93% were White, and ages ranged from 12 to 82 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the trial, no systemic allergic (type I hypersensitivity) reactions were reported. Other systemic reactions were reported by 1 (2%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of other systemic reaction was multifocal skin reaction experienced on the day of dosing.

(continued on next page)

6 ADVERSE REACTIONS *(cont'd)*

Injection Site Reactions
Injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving 300 mg of NUCALA compared with 4% in patients receiving placebo.

6.5 Immunogenicity
In adult and adolescent patients with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 patient with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 or 100 mg, 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.
In patients with CRSwNP receiving NUCALA 100 mg, 6/196 (3%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with CRSwNP.
In patients with EGPA receiving 300 mg of NUCALA, 1/68 (<2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with EGPA.
In adult and adolescent patients with HES receiving 300 mg of NUCALA, 1/53 (2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with HES.
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.

6.6 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 subcutaneous (*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.

8.4 Pediatric Use
Severe Asthma
The safety and efficacy of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older.
Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT01691521) and had a mean age of 14.8 years. Patients had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1) of full prescribing information.]* Patients had a reduction in the rate of exacerbations that trended in favor of NUCALA. Of the 19 adolescents who received NUCALA, 9 received 100 mg and the mean apparent clearance in these patients was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.
Use of NUCALA in pediatric patients aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single, open-label clinical trial (NCT02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg subcutaneous every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg SC *[see Clinical Pharmacology (12.3) of full prescribing information]*.
The effectiveness of NUCALA in pediatric patients aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents *[see Clinical Pharmacology (12.3) of full prescribing information]*. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2) of full prescribing information]*. The safety and effectiveness in pediatric patients aged younger than 6 years with severe asthma have not been established.
Chronic Rhinosinusitis with Nasal Polyps
The safety and effectiveness in patients aged younger than 18 years with CRSwNP have not been established.
Eosinophilic Granulomatosis with Polyangiitis
The safety and effectiveness in patients aged younger than 18 years with EGPA have not been established.
Hypereosinophilic Syndrome
The safety and effectiveness of NUCALA for HES have been established in adolescent patients aged 12 years and older. The safety and effectiveness in pediatric patients aged younger than 12 years with HES have not been established.
Use of NUCALA for this indication is supported by evidence from an adequate and well-controlled study (NCT02836496) in adults and adolescents and an open-label extension study (NCT03306043). One adolescent received NUCALA during the controlled study and this patient and an additional 3 adolescents received NUCALA during the open-label extension study *[see Clinical Studies (14.4) of full prescribing information]*. The 1 adolescent treated with NUCALA in the 32-week trial did not have a HES flare or an adverse event reported. All adolescents received 300 mg of NUCALA for 20 weeks in the open-label extension.

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of patients aged 65 years and older that received NUCALA (n = 79) to determine whether they respond differently from younger patients. 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
There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

17 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, 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)]*.

Manufactured by
GlaxoSmithKline LLC
Philadelphia, PA 19112
U.S. License Number 1727

Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised: 7/2021 NCL:7BRS

MPLJRNA210001 August 2021
Produced in USA.

CHEST in the news

BY LAURA DIMASI
CHEST PR and Communications Specialist

Creating a stronger voice for CHEST members in pulmonary, critical care, and sleep medicine, CHEST works to provide opportunities for members to serve as expert sources for both mainstream and trade media.

Below are a few highlights of media coverage from the past few months that work to expand awareness of CHEST and to promote the expertise of CHEST members in the media.

The *New York Times* covers the Philips recall

In August, a *New York Times* article quoted incoming CHEST President, David Schulman, MD, MPH, FCCP. The article covered the recent Philips recall and its impact on the COVID-19 pandemic.

Dr. Schulman is quoted saying, "Because the number of people coming into the hospital with severe respiratory symptoms has increased as a result of COVID-19, the demand for these devices has also increased, which is problematic since available supply has decreased as a result of the Philips recall."

The full article, *Breathing Machine Recall Over Possible Cancer Risk Leaves Millions Scrambling for Substitutes*, can be found on the New York Times website.

Technical expert panel on coverage determinations

Peter Gay, MD, FCCP, was quoted in an article by *McKnight's Long-Term Care News* on the recent technical expert panel recommendations for national coverage determinations for optimal noninvasive ventilation.

"Centers for Medicare & Medicaid Services was wanting rigorous scientific support necessary to clarify the 'reasonable and necessary' role of these new mechanical therapeutic modalities where there was none in order to move forward," said Dr. Gay. "What we have done is create a pathway to simplify the maze of regulation and perhaps most importantly, remove the obstacles that currently exist."

The full article, *Panel on Non-Invasive Ventilation Seeks to Simplify 'Maze' of Regulation for Device Coverage*, can be found on the *McKnight's Long-Term Care News* website.

Asthma and HRT

Originally appearing in *Healthday*, *U.S. News and World Report* covered a recent journal *CHEST*® publication *Hormone Replacement Therapy and Development of New Asthma* by Erik Soeren Halvard Hansen, MD, et al.

The study included about 34,500 women who were diagnosed with asthma between 1995 and 2018, when they were 40 to 65 years of age. Each was then compared with 10 asthma-free women.

Based on that comparison, HRT use was associated with a 63% higher risk for developing asthma, according to the study.

The full article, *HRT Could Raise Odds for Asthma*, can be found on the *U.S. News & World Report* website.

Pediatric ICU admission and COVID-19

Healio Pulmonology covered a re-

Thank you for your continued support of the CHEST Foundation! With the generous donations we receive from members such as yourself, we can provide funding to members in our community in the form of multiple grants, such as research, community service, and diversity. Without you, none of these grants would be possible!

2021 RESEARCH GRANT RECIPIENTS

CHEST Foundation Research Grant in Lung Cancer
Daniel Ryan, MD
Royal College of Surgeons Ireland, Dublin, Ireland

CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
Miguel Divo, MD
Brigham and Women's Hospital, Boston, MA

Stephen Milne, MBBS
Woolcock Institute of Medical Research
Vancouver, BC, Canada

CHEST Foundation Research Grant in Critical Care
Jacqueline Stocking, PhD
University of California, Davis, Davis, CA

CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
John Charles Rotondo, PhD
University of Ferrara, Ferrara, Italy

CHEST Foundation Research Grant in Nontuberculous Mycobacteria Diseases
Edward Chan, MD
Rocky Mountain Regional Veterans Affairs Medical Center, Denver, CO

CHEST Foundation Research Grant in Cystic Fibrosis
Shahid Sheikh, MD, FCCP
Nationwide Children's Hospital, Columbus, OH

John R. Addrizzo, MD, FCCP Research Grant in Sarcoidosis
Maneesh Bhargava, MD, PhD, FCCP
Minneapolis VA Health Care System
Minneapolis, MN

CHEST Foundation Research Grant in Severe Asthma
Felix Reyes, MD
Montefiore Medical Center, Bronx, NY

CHEST Foundation Research Grant in Pulmonary Fibrosis
Marco Mura, MD, PhD
Western University, London, Ontario, Canada

Janelle Pugashetti, MD
University of California, Davis, Davis, CA

CHEST Foundation Research Grant in Pulmonary Hypertension
Michael Lee, MD
University of California San Francisco
San Francisco, CA

Navneet Singh, MD
Warren Alpert School of Medicine at Brown University, Providence, RI

CHEST Foundation Research Grant in Sleep Medicine
Shahid Karim, MBChB
Mayo Clinic, Rochester, MN

Thomas Tolbert, MD
Mount Sinai Hospital, New York, NY

CHEST Foundation and American Academy of Sleep Medicine Foundation Research Grant in Sleep Medicine
Marta Kaminska, MD
McGill University Health Centre, Montreal, QC, Canada

CHEST Foundation and APCCMPD Research Grant in Medical Education
Mark Adelman, MD
NYU School of Medicine, New York, NY

CHEST Foundation Research Grant in COVID-19
Marlene Cano, MD, PhD
Washington University, St. Louis, MO

Brandon Walsh, MD
New York University, New York, NY

CHEST Foundation and ATS Research Grant in COVID-19 and Diversity
Navitha Ramesh, MD, FCCP
UPMC Harrisburg, Harrisburg, PA

Inderjit Singh, MBBCh
Yale University, New Haven, CT

cent journal *CHEST* publication, *Changes in Pediatric ICU Utilization and Clinical Trends During the Coronavirus Pandemic*, by Janine E. Zee-Cheng, MD, et al.

"Severe infections, traumatic injuries, perioperative conditions and acute exacerbations of chronic illnesses such as asthma and diabetes are among the most common causes of admission to a pediatric ICU; thus, the epidemiology of pediatric critical illness was likely sensitive to the indirect effects of COVID-19," Janine E. Zee-Cheng, MD, adjunct clinical assistant professor of pediatrics in the department of pediatrics at Indiana University School of Medicine, Indianapolis, and colleagues wrote.

The full article, *Pediatric ICU admissions significantly decreased during COVID-19 pandemic*, can be found on the *Healio* website.

CHEST news

CHEST also recently issued a handful of statements and press releases on a variety of topics including the spread of misinformation, support of mandatory vaccinations for health care workers, and a statement advocating for broader coverage of supplemental oxygen use.

For all recent CHEST News, including these statements, visit the CHEST Newsroom on the CHEST website (https://www.chestnet.org/Newsroom) and follow the hashtag #CHESTNews on Twitter.

If you have been included in a recent news article and would like it to be featured, send the coverage to media@chestnet.org.

2021 COMMUNITY SERVICE GRANT RECIPIENTS

CHEST Foundation Community Service Grant
Honoring D. Robert McCaffree, MD, Master FCCP

Valerie Andrews, BS
The JUDAHH Project, Sacramento, CA

Chanda Holsey, DrPh
National Medical Association, Silver Spring, MD

Arzu Ari, PhD, FCCP
Texas State University, San Marcos, TX

Panagis Galiatsatos, MD, MPH
John Hopkins University, Baltimore, MD

Patricia George, MD
National Jewish Health, Denver, CO

Nishant Gupta, MD, MS
University of Cincinnati, Cincinnati, OH

Syed Naqvi, MD, MBBS
Hoag Hospital Newport Beach
Newport Beach, CA

To learn about the projects from this year's research and community grant recipients, please visit chestnet.org/grants.

CHEST FOUNDATION DIVERSITY GRANT RECIPIENTS

The CHEST Foundation is pleased to announce the recipients of the 2021 Diversity Grant. Diversity Grants are awarded to those who represent underrepresented minorities, outstanding trainees, and early-career clinicians (completed training within previous 5 years).

These individuals were nominated by a member of leadership and will receive complimentary registration to the CHEST 2021 Annual Meeting.

Aparna Balasubramanian, MD, MHS
Dhishna Chaudhary, MD
Jeremy Courtney, MD
Aunie Danyalian, MD
Meghana Dasyam, MBBS
Akash Dodia, MBBS, DTCD
Ahmed El Maghraby, MD, MBBCh
Sangeetha Isaac, MD
Lisa Jarnagin, MBBCh
Saminder Kalra, MD
Amos Lal, MBBS
Aravind Menon, MD
Thais Ribeiro Peclat Monteiro, MD, PhD
LaShanda Penn, RN, MSN
Ariella Pratzer, MD
Rizwana Rana, MBBS
Ann Rusk, MD
Ashley Scott, MD
Pahnwat Tonya Taweesedt, MD
Polina Trachuk, MD
Ranuka Sinniah, MD
Navneet Singh, MD
Musaib Ahmed Syed, MD, MBBS
Muhammad Khyzar Hayat Syed, MBBS
Jaleesa Watkins
Catherine Wegner Wippel, MD
Nadia Yimer, MD

CHEST FOUNDATION

Your support directly impacts future grant recipients.
Become a part of the CHEST Foundation's Champion's Circle, donate today at **chestfoundation.org/donate**.

In memoriam

Ronald B. George, MD, Master FCCP

Past President (1993-1994) of the American College of Chest Physicians, Dr. Ronald Baylis George died July 19, 2021, in Shreveport, Louisiana. He was an active and respected leader for the College for many years. Dr. George was

Dr. Ronald B. George

Professor Emeritus of Medicine and former Chairman of the Department of Medicine, School of Medicine, Louisiana State University, Shreveport. He founded the Pulmonary and Critical Care Division at LSU and then served as Chief for many years. Dr. George was an outstanding clinician and a nationally recognized leader in the field of pulmonary diseases. He had a special gift for diagnosing difficult lung disease cases and was constantly sought out by residents, staff, and physicians for his help with patients. He was a visiting professor at many academic institutions throughout the country. As a prolific writer, Dr. George authored over 200 manuscripts, books, and book chapters, including one of the most successful, longstanding pulmonary textbooks, Chest Medicine, now in its 5th edition. CHEST extends heartfelt condolences to the George family.

Wearable sensors detect viral infections before symptoms

BY PAM HARRISON

A simple wristband containing biometric monitoring sensors is able to pick up early infection from both influenza and the common cold before symptoms develop. Moreover, it can predict the severity of the illness once it becomes symptomatic, new research shows.

"Prior to the development of symptoms, people are still infectious and can potentially infect others," senior author Jessilyn Dunn, PhD, Duke University, Durham, N.C., told this news organization.

"That's why it's so important to be able to detect infection even when a person doesn't feel symptomatic, as this would help prevent the spread of pathogens that occur before somebody knows they are sick – and which is why it is important from a public health perspective," she added.

The study was published online Sept. 29, 2021, in JAMA Network Open (doi: 10.1001/jamanetworkopen.2021.28534).

Two challenge studies

The study involved 31 participants who were inoculated with the H1N1 influenza virus and 18 others who were inoculated with rhinovirus. The rhinovirus challenge study was conducted in 2015, and the H1N1 challenge study was carried out in 2018. Both groups of patients were inoculated via intranasal drops of either the diluted H1N1 virus or the diluted rhinovirus strain type 16.

Participants in both challenge studies wore the E4 wristband (Empatica). Those in the influenza study wore the wristband 1 day before and 11 days after being inoculated, and those in the rhinovirus study wore the wristband for 4 days before and 5 days after inoculation. The E4 wristband measures heart rate, skin temperature, electrodermal activity, and movement.

Symptoms were typical of each infection and were classified as both observable events, such as runny nose, cough, and wheezy chest, or unobservable events, such as muscle soreness and fatigue. Infection status was classified as asymptomatic or noninfectious (AON), mild, or moderate.

The biosensors contained within the wristband were able to detect the presence or absence of H1N1 infection with an accuracy of 79% within 12 hours after participants had been inoculated and an accuracy of 92% within 24 hours of being inoculated, the authors report. Thus, "we could assess whether or not a participant was infected with H1N1 between 24 and 36 hours before symptom onset," the investigators noted.

The median time for symptom onset following the rhinovirus challenge was 36 hours after inoculation. The biosensors predicted the presence or absence of rhinovirus infection with an accuracy of 88%, the authors wrote. And when both viral challenges were combined, models predicting infection had an accuracy of 76% at 24 hours after participants being inoculated.

Prediction of severity

Twelve hours after participants were inoculated, the technology was also able to predict the development of either AON or moderate H1N1 infection with 83% accuracy. For rhinovirus, the predictive accuracy of distinguishing AON versus moderate infection was slightly higher at 92% whereas for both viruses combined, the technology predicted the development of AON versus moderate infection with 84% accuracy rate.

As the authors pointed out, the ability to identify individuals during the early critical stage of viral infection could have wide-ranging effects. "In the midst of the global SARS-CoV-2 pandemic, the need for novel approaches like this has never been more apparent," they suggested.

And in point of fact, in a not-yet peer-reviewed study using a real-time smartwatch-based alerting system again designed to detect aberrant physiologic and activity signals associated with early infection (medRxiv. 2021 Jun 21. doi: 10.1101/2021.06.13.21258795), Stanford (Calif.) University investigators found that alerts were generated for presymptomatic and asymptomatic COVID-19 infections in 78% of cases in over 3,200 participants tested at a median of 3 days prior to symptom onset.

The authors also noted that their system is scalable to millions of users, thus offering a personal health

Continued on following page

Continued from previous page

monitoring system that can operate in real time.

In a comment, Steven Steinhubl, MD, a research scientist and formerly the director of digital medicine at Scripps Research's Translational Institute, La Jolla, Calif., told this news organization that he personally has a lot of faith in this type of technology.

"Unfortunately, COVID-19 has changed our perspective about respiratory infections but if you think of the bad flu seasons we've had in the past, people do die from influenza, so I think there is a lot of value [in this technology], although the degree of value depends on the severity of the infection," Dr. Steinhubl said.

For example, if people actually ever go back into work together, early recognition that an employee might have influenza or another highly contagious infection could alert them to the necessity to stay home and self-isolate.

"We have a bit to go before we get there," Dr. Steinhubl acknowledged, "but you could have a really big impact on the spread of any infectious disease that would be better for everybody."

Dr. Dunn has disclosed no relevant financial relationships. Dr. Steinhubl is chief medical officer at physIQ, a company involved in the development of personalized analytics.

Remdesivir may lower COVID hospitalization risk

BY MARCIA FRELLICK

Treatment with remdesivir (Veklury, Gilead) was found to reduce some COVID-19 patients' risk of hospitalization by 87% in a phase 3 trial, the drug's manufacturer announced in a press release.

The randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of a 3-day course of intravenous remdesivir in an analysis of 562 nonhospitalized patients who were at high risk for COVID-19 disease progression.

Remdesivir demonstrated a statistically significant 87% reduction in risk for COVID-19–related hospitalization or all-cause death by day 28 (0.7% [2/279]) compared with placebo

Continued on following page

Continued from previous page

(5.3% [15/283]) *P* = .008. Participants were assigned 1:1 to remdesivir or the placebo group.

Researchers also found an 81% reduction in risk for the composite secondary endpoint – medical visits due to COVID-19 or all-cause death by day 28. Only 1.6% had COVID-19 medical visits (4/246) compared with those in the placebo group (8.3% [21/252]) *P* = .002. No deaths were observed in either arm by day 28.

"These latest data show remdesivir's potential to help high-risk patients recover before they get sicker and stay out of the hospital altogether," coauthor Robert L. Gottlieb, MD, PhD, from Baylor University Medical Center, Houston, said in the press release.

Remdesivir is the only drug approved by the U.S. Food and Drug Administration for hospitalized COVID-19 patients at least 12 years old.

Its treatment of nonhospitalized patients with 3 days of dosing is still investigational, and the safety and the efficacy for this use and dosing duration have not been established or approved by any regulatory agency, according to the Gilead press release.

The patients in this study were considered high risk for disease progression based on comorbidities – commonly obesity, hyper-

tension, and diabetes – and age, but had not recently had hospitalizations due to COVID-19.

A third of the participants were at least 60 years old. All of the participants in the study must have received a positive diagnosis within 4 days of starting treatment and experienced symptoms for 7 days or less in order to be included.

Use of remdesivir controversial

Results from the Adaptive COVID-19 Treatment Trial (ACTT-1) showed remdesivir was superior to placebo in shortening time to recovery in adults hospitalized with COVID-19 with evidence of lower respiratory tract infection.

However, a large trial of more than 11,000 people in 30 countries, sponsored by the World Health Organization, did not show any benefit for the drug in reducing COVID deaths.

The WHO has conditionally recommended against using remdesivir in hospitalized patients, regardless of disease severity, "as there is currently no evidence that remdesivir improves survival and other outcomes in these patients," the organization inidcated.

The drug also is given intravenously, and this study tested three infusions over 3 days, a difficult treatment for nonhospitalized patients.

The study results were released ahead of IDWeek.

Gastrointestinal Perforation [*see Warnings and Precautions*].
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. The safety of OFEV was evaluated in over 1000 IPF patients, 332 patients with chronic fibrosing ILDs with a progressive phenotype, and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials. Idiopathic Pulmonary Fibrosis: OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).
Combination with Pirfenidone: Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone. Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) [*see Warnings and Precautions*]. Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype: OFEV was studied in a phase 3, double-blind, placebo-controlled trial (Study 5) in which 663 patients with chronic fibrosing ILDs with a progressive phenotype were randomized to receive OFEV 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks. At 52 weeks, the median duration of exposure was 12 months for patients in both treatment arms. Subjects ranged in age from 27 to 87 years (median age of 67 years). The majority of patients were Caucasian (74%) or Asian (25%). Most patients were male (54%). The most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of patients treated with OFEV and in 5% of patients treated with placebo. No pattern was identified in the adverse events leading to death. Adverse reactions leading to permanent dose reductions were reported in 33% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (16%). Adverse reactions leading to discontinuation were reported in 20% of OFEV-treated patients and 10% of placebo-treated patients. The most frequent adverse reaction that led to discontinuation in OFEV-treated patients was diarrhea (6%). The safety profile in patients with chronic fibrosing ILDs with a progressive phenotype treated with OFEV was consistent with that observed in IPF patients. In addition, the following adverse events were reported in OFEV more than placebo in chronic progressive fibrosing ILD: nasopharyngitis (13% vs. 12%), upper respiratory tract infection (7% vs 6%), urinary tract infection (6% vs. 4%), fatigue (10% vs. 6%), and back pain (6% vs. 5%). Systemic Sclerosis-Associated Interstitial Lung Disease: OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSc-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate. The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs 1.7% placebo) and pneumonia (2.8% nintedanib vs 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm. Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%). Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%). The safety profile in patients with or without mycophenolate at baseline was comparable. The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain[a]	18%	11%
Liver enzyme elevation[b]	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension[c]	5%	2%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.
[b] Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.
[c] Includes hypertension, blood pressure increased, and hypertensive crisis

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. 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. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury *[see Warnings and Precautions]*, non-serious and serious bleeding events, some of which were fatal [*see Warnings and Precautions*], pancreatitis, thrombocytopenia, rash, pruritus.

7 DRUG INTERACTIONS: 7.1 P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV *[see Dosage and Administration]*. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **7.2 Anticoagulants:** Nintedanib is a VEGFR inhibitor and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [*see Warnings and Precautions*]. **7.3 Pirfenidone:** In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone. **7.4 Bosentan:** Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and

Portal use gives patients access, doctors headaches

BY KEN TERRY

The use of patient portals that provide access to electronic health records has dramatically increased in the past several years, and patients whose health care practitioner encouraged them to use their online portal accessed them at a higher rate than those who were not encouraged to do so.

These were among the top-line results of a national survey of U.S. adults conducted by the National Institutes of Health from January 2020 to April 2020. Although the COVID-19 pandemic hit the United States in the middle of that period, a report on the survey by the Office of the National Coordinator for Health IT stated, "These findings largely reflect prepandemic rates of individuals being offered and subsequently using their online medical record, also known as a patient portal."

But with more patient access can come additional work for physicians and other health care practitioners, ranging from an onslaught of patient communications to managing data sent to them by patients.

According to the report, 59% of individuals were offered access to their patient portal, and 38% accessed their record at least once in 2020. By comparison, in 2014, just 42% were offered access to their portal, and 25% used it. But these percentages hardly changed from 2019 to 2020.

But with more patient access can come additional work for physicians and other health care practitioners, ranging from an onslaught of patient communications to managing data sent to them by patients.

The increase in the percentage of people who accessed portals reflects the fact that more people were offered access. In addition, there were signs of rising activity among portal users.

Among patients offered access to their patient portal, 64% accessed it at least once in 2020 – 11 percentage points more than in 2017. Twenty-seven percent of those who had access to a portal used it once or twice; 20% accessed it three to five times; and 18% used it six or more times. The latter two percentages were significantly higher than in 2017.

Of the respondents who were offered access to portals but didn't use them, 69% said they didn't access the portal because they preferred to speak with their health care practitioner directly. Sixty-three percent said they didn't see a need to use their online medical record. This was similar to the percentage 3 years earlier. Other reasons included respondents' concerns about the privacy/security of online medical records (24%), their lack of comfort with computers (20%), and their lack of Internet access (13%).

The pros and cons of patient portals, greater access

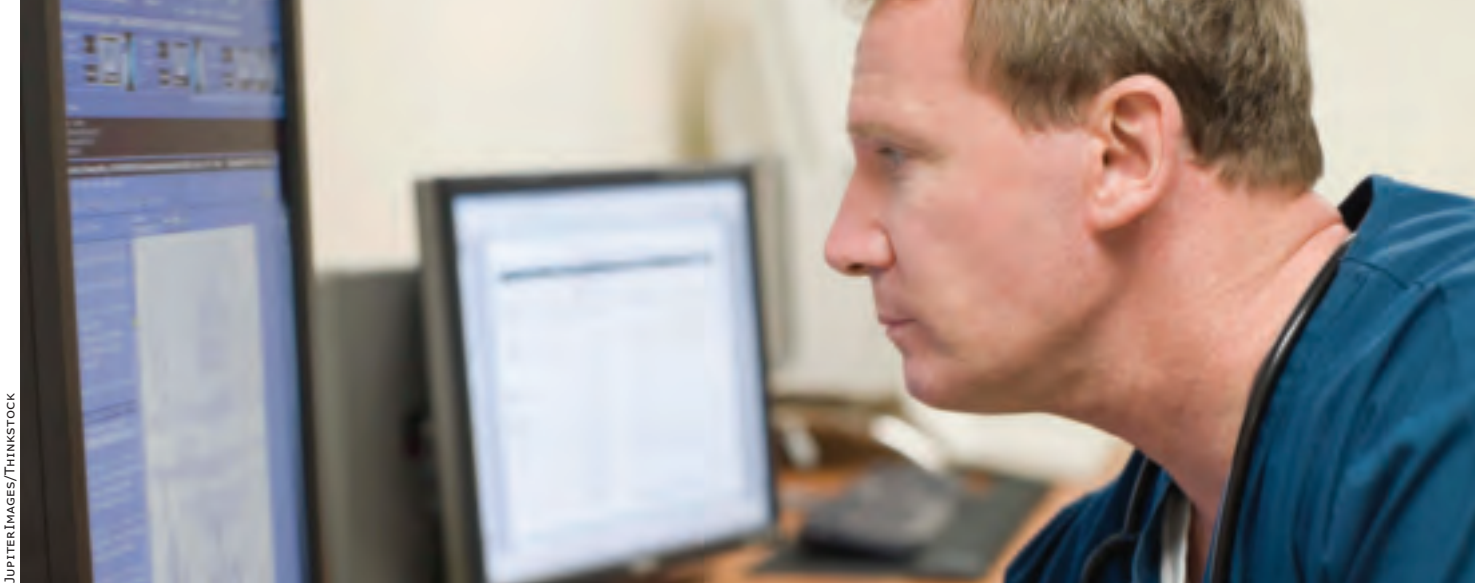
Among portal users who accessed their records through a mobile health app, 51% used the app to facilitate discussions with their health care practitioner in 2020, an 8–percentage point increase from 2017. Fifty-percent of the mobile health app users utilized it to make a decision about how to treat an illness or condition, up from 45% in 2017. And 71% of these individuals used their app to track progress on a health-related goal, just a bit more than in 2017.

Individuals who were encouraged by their health care practitioner to use their patient portal viewed clinical notes and exchanged secure messages with their practitioner at higher rates than those who had not been encouraged. This is not surprising, but it reflects an unintended result of patient portals that many physicians have found burdensome, especially during the pandemic: overflowing electronic in-boxes.

Robert Wachter, MD, chairman of the department of medicine at the University of California, San Francisco, recently tweeted, "We're seeing huge uptick in in-box messages for MDs during COVID – now seems like biggest driver of MD burnout. The fundamental problem: We turned on 24/7/365 access for patients (who of course like it) with no operational or business model to handle it. Crucial that we fix this."

Steven Waldren, MD, vice president and chief medical informatics officer at the American Academy of Family Physicians, told this news organization that he agrees that this is a major challenge. "In-box management is a burden on physicians and practices," he said. "However, it can be done better, either through a team in-box or through better use of technology."

The team in-box he refers to is a mechanism for triaging patient messages. For example, a triage nurse can look at the messages and decide which ones can be handled by staff and which ones the doctor needs to see. Or physicians and front office staff can see the messages at the same time; a nurse can triage some messages according to protocols, and the physician can respond to any message, depending on what he or she knows about the patient.



JupiterImages/Thinkstock

Technology can also be enlisted in the effort, he suggested, perhaps by automating the triaging of messages such as prescription refill requests or using artificial intelligence to sort messages by content.

Making patient records portable

Nearly 40% of portal users accessed it using a smartphone app (17%) or with both their smartphone app and their computer (22%). Sixty-one percent of users relied exclusively on computers to access their portals.

About a third of patient portal users downloaded their online medical records in 2020. This proportion has nearly doubled from 17% since 2017, the ONC report noted.

Although the survey didn't ask about multiple downloads, it appears that most people had to download their records separately from the patient portal of each practitioner who cared for them. Although the Apple Health app allows people to download records to their iPhones from multiple portals using a standard application programming interface, the ONC report says that only 5% of respondents transmitted their records to a service or app, up slightly from 3% in 2017.

Dr. Waldren hopes most patients will have the ability to download and integrate records from multiple practitioners in a few years, but he wouldn't bet on it.

"A fair amount of work needs to be done on the business side and on figuring out how the data get connected together," he said. "And there are still privacy concerns with apps."

Overall, 21% of portal users transmitted their data to at least one outside party in 2020, compared with 14% in 2017. Seventeen percent of them sent their records to another health care practitioner, up from 10% in 2017. Five percent of the users transmitted their records to a caregiver, slightly more than in 2017.

Managing data is a challenge

Asked how physicians feel about portal users adding information to their record or correcting inaccurate information, Dr. Waldren says, "Doctors are already comfortable with patient-generated data. The challenge is managing it. If the patient provides data that's not easy to put in the EHR, that's going to add work, and they don't want to see 100 blood pressure readings.

"You'd be hard-pressed to find a doctor who doesn't welcome additional information about the patient's health, but it can be onerous and can take time to enter the data," Dr. Waldren said.

Overall, he said, "Giving patients the ability to take more ownership of their health and participate in their own care is good and can help us move forward. How this will be integrated into patient care is another question."

INDEX OF ADVERTISERS

Nucala
(mepolizumab)

Bring on today.

See the options at
NUCALAAutoinjector.com

NUCALA
Autoinjector

gsk