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Columbia University Irving Medical Center

Beyond cystic fibrosis: Genetics of PF and other lung diseases

BY CHRISTINE KILGORE

MDedge News

The remarkable story of cystic fibrosis (CF) – from gene discovery in 1989 to highly effective precision-medicine therapies today – inspires Christine Kim Garcia, MD, PhD, as she searches for rare mutations in genes linked to inherited forms of lung fibrosis, termed familial pulmonary fibrosis (FPF).

"Cystic fibrosis has provided a framework for approaching the genetics of lung fibrosis," said Dr. Garcia, Frode Jensen Professor of Medicine and chief of the pulmonology, allergy, and critical care medicine division at Columbia University, and director of the Columbia Precision

Medicine Initiative, both in New York.

Pulmonary fibrosis is more complicated than CF. "Mutations in more than 10 different genes can lead to the increased heritable risk of pulmonary fibrosis that we find in families. Different mutations exist for each gene. Sometimes the mutations are so rare that they are only found in a single family," she said. "In addition, different subtypes of fibrotic interstitial lung disease can be linked to the same mutation and found in the same family."

Despite these complexities, genetic discoveries in PF have illuminated pathophysiologic pathways and are driving the research that Dr. Garcia and other experts hope will lead to

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Sepsis too often neglected in hospitals

BY MARCIA FRELLICK

More than 1,400 hospitals in the United States do not have a sepsis program to lead the intervention for a medical emergency that affects at least 1.7 million people, according to a recent survey by the Centers for Disease Control and Prevention.

For the hospitals that do have sepsis teams, only 55% of them report that their team leaders get dedicated time to manage their sepsis programs.

"One in three people who dies in a hospital has sepsis during that hospitalization," CDC Director Mandy Cohen, MD, MPH, noted in a statement. "That's why CDC is calling on all U.S. hospitals to have a sepsis program and raise the bar on sepsis care by incorporating seven core elements."

The sepsis seven

- Leadership: Dedicating the necessary human, financial, and information technology resources.
- Accountability: Appointing a leader responsible for program outcomes and setting concrete goals.
- Multiprofessional: Engaging key partners

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INSIDE HIGHLIGHT



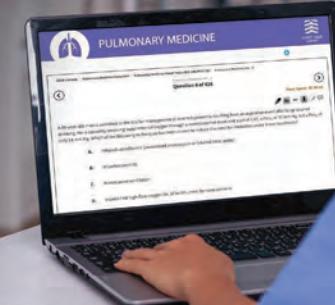
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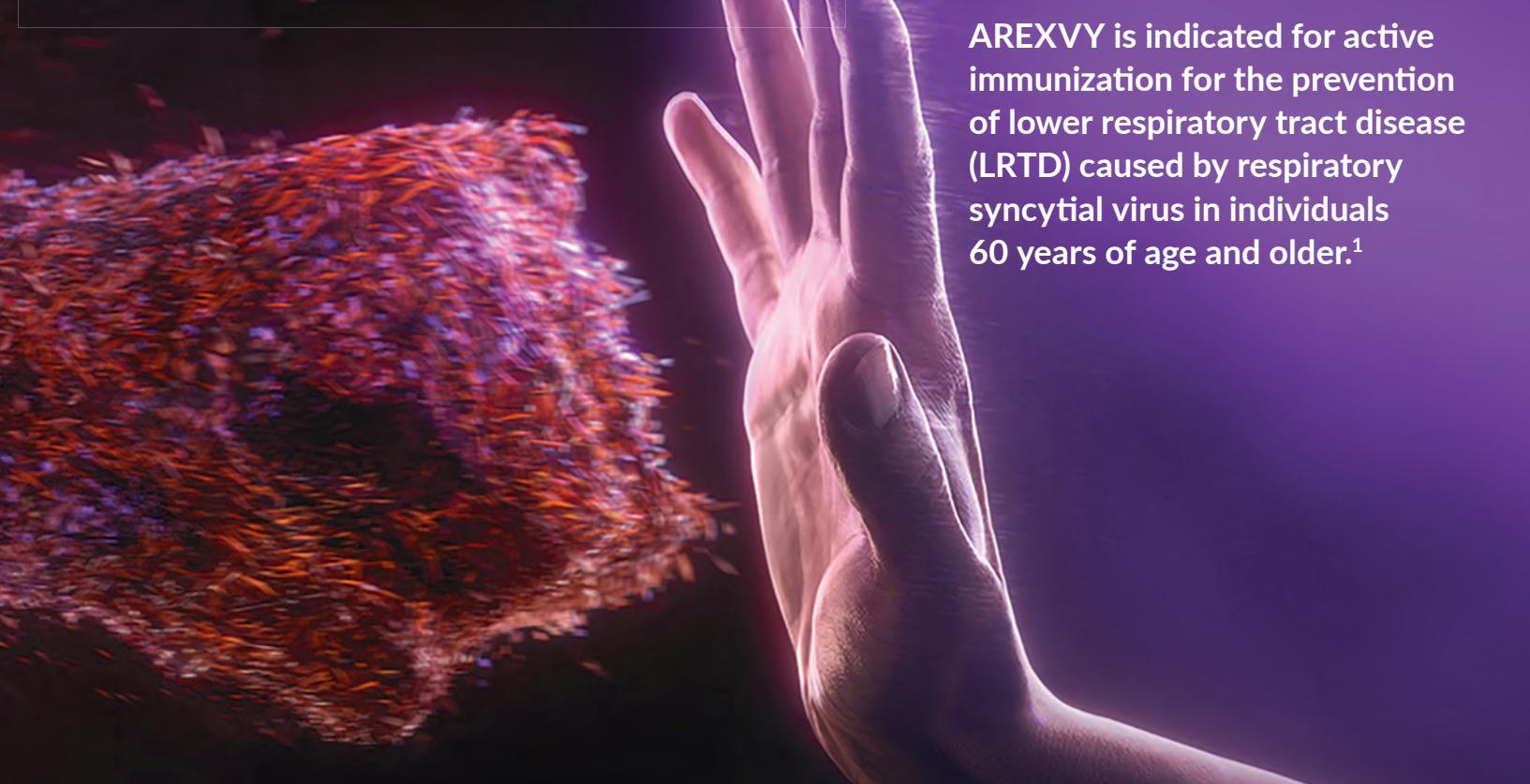
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Study for Board Review on the Go With SEEK

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RSV STOPS HERE



AREXVY is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in individuals 60 years of age and older.¹

Vaccination may not protect all recipients.¹

Learn more at AREXVYhcp.com



Important Safety Information

- AREXVY is contraindicated in anyone with a history of a severe allergic reaction (eg, anaphylaxis) to any component of AREXVY
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of AREXVY
- Syncope (fainting) may occur in association with administration of injectable vaccines, including AREXVY. Procedures should be in place to avoid injury from fainting

Please see additional Important Safety Information to the right.

RSV=respiratory syncytial virus.

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RSAJRNA230011 May 2023
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AREXVY Is Proven to Protect Adults Aged 60 Years and Older From RSV-LRTD¹

PRIMARY ENDPOINT

82.6%

**OVERALL EFFICACY
AGAINST RSV-LRTD
(96.95% CI, 57.9, 94.1)**

AREXVY (7 cases out of 12,466),
placebo (40 cases out of 12,494)

SECONDARY ENDPOINT

94.6%

**EFFICACY AGAINST RSV-LRTD
IN PARTICIPANTS WITH AT LEAST
1 COMORBIDITY* (95% CI, 65.9, 99.9)**

AREXVY (1 case out of 4937),
placebo (18 cases out of 4861)

*Comorbidities of Interest

Chronic obstructive pulmonary disease (COPD), asthma, any chronic respiratory/pulmonary disease, chronic heart failure, diabetes mellitus type 1 or type 2, and advanced liver or renal disease.

Study Design¹:

Study 1, an ongoing, phase 3, randomized, placebo-controlled, observer-blind study in adults aged ≥ 60 years, evaluated the efficacy of AREXVY in preventing RSV-LRTD during the first season. Participants in the primary population for efficacy analysis received 1 dose of AREXVY (n=12,466) or placebo (n=12,494). At the time of this analysis, median follow-up was 6.7 months.

LRTD was defined as ≥ 2 lower respiratory symptoms/signs, including ≥ 1 lower respiratory sign for at least 24 hours, or ≥ 3 lower respiratory symptoms for at least 24 hours.

Important Safety Information (cont.)

- Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to AREXVY
- The most commonly reported adverse reactions ($\geq 10\%$) were injection site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), and arthralgia (18.1%)
- Vaccination with AREXVY may not result in protection of all vaccine recipients

Please see Brief Summary of full Prescribing Information for AREXVY on adjacent pages.

Reference: 1. Prescribing Information for AREXVY.

AREXVY
(RESPIRATORY SYNCYTIAL VIRUS
VACCINE, ADJUVANTED)

BRIEF SUMMARY

AREXVY (Respiratory Syncytial Virus Vaccine, Adjuvanted)

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

1 INDICATIONS AND USAGE

AREXVY is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in individuals 60 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dose and Schedule

Administer a single dose (0.5 mL) of AREXVY as an intramuscular injection.

2.3 Administration

For intramuscular injection only.

After reconstitution, administer AREXVY immediately or store protected from light in the refrigerator between 2°C and 8°C (36°F to 46°F) or at room temperature [up to 25°C (77°F)] and use within 4 hours. Discard reconstituted vaccine if not used within 4 hours.

4 CONTRAINDICATIONS

Do not administer AREXVY to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of AREXVY [see Description (11) of full prescribing information].

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Vaccine Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of AREXVY.

5.2 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines, including AREXVY. Procedures should be in place to avoid injury from fainting.

5.3 Altered Immunocompetence

Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to AREXVY.

6 ADVERSE REACTIONS

In a clinical trial (NCT04886596), the most commonly reported ($\geq 10\%$) adverse reactions were injection site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), and arthralgia (18.1%).

6.1 Clinical Trials Experience

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

The safety of AREXVY was evaluated in 15,845 vaccine recipients.

Study 1 (NCT04886596) is a placebo-controlled, Phase 3 clinical study conducted in Europe, North America, Asia, and the Southern Hemisphere (South Africa, Australia, and New Zealand), involving 24,966 participants, 60 years of age and older, who received AREXVY (n = 12,467) or saline placebo (n = 12,499). Study 2 (NCT04732871) is a non-placebo-controlled, open-label, Phase 3 clinical study conducted in Europe, North America, and Asia, involving 1,653 participants, 60 years of age and older, who received AREXVY. Study 3 (NCT04841577) is a non-placebo-controlled, open-label, Phase 3 clinical study conducted in New Zealand, Panama, and South Africa, involving participants 60 years of age and older who received 1 dose of AREXVY and FLUARIX QUADRIVALENT concomitantly (n = 442) or sequentially (n = 443).

At the time of vaccination in Study 1, the median age of the population was 69.0 years; 13,943 (55.8%) participants were 60 to 69 years of age, 8,978 (36.0%) participants were 70 to 79 years of age, and 2,045 (8.2%) participants were 80 years of age and older. The majority of participants were White (79.4%), followed by Black (8.7%), Asian (7.6%), and other racial/ethnic groups (4.3%); 5.5% were of Hispanic or Latino ethnicity; 51.7% were female. In Study 2, the median age of the population at the time of vaccination was 69.0 years; 820 (49.6%) participants were 60 to 69 years of age, 621 (37.6%) participants were 70 to 79 years of age, and 212 (12.8%) participants were 80 years of age and older. In Study 2, the majority of participants were White (67.8%), followed by Asian (30.0%), Black (2.0%), and other racial/ethnic groups (0.2%); 1.9% were of Hispanic or Latino ethnicity; 54.6% were female. In Study 3, the median age of the population at the time of the vaccination was 67.0 years; 519 (58.6%) participants were 60 to 69 years of age, 288 (32.5%) participants were 70 to 79 years of age, and 78 (8.8%) participants were 80 years of age and older, respectively. In Study 3, the majority of the participants were of mixed race (50.3%), followed by White (30.7%), and Black (16.0%); 34.7% were of Hispanic or Latino ethnicity; 51.5% were female.

Safety Data from Study 1

Solicited Adverse Reactions: In Study 1, a subset of study participants (solicited safety set) was monitored for solicited adverse reactions using standardized paper diary cards during the 4 days (i.e., day of vaccination and the next 3 days) following a dose of AREXVY or placebo; 879 participants received AREXVY and 874 participants received placebo. The other study participants did not prospectively record solicited reactions on a diary card but may have reported them as unsolicited adverse reactions.

The reported frequencies of specific solicited local (administration site) and systemic adverse reactions (per participant) are presented in Table 1.

Table 1. Percentage of Participants with Solicited Local Adverse Reactions and Systemic Adverse Reactions within 4 Days of Vaccination in Adults 60 Years of Age and Older (Solicited Safety Set with 4-Day Diary Card)

Local Adverse Reactions	AREXVY % N = 879	Placebo ^a % N = 874
Pain, Any ^b	60.9	9.3
Pain, Grade 3 ^b	1	0
Erythema, >20 mm	7.5	0.8
Erythema, >100 mm	0.2	0
Swelling, >20 mm	5.5	0.6
Swelling, >100 mm	0.2	0
Systemic Adverse Reactions	N = 879	N = 878
Fatigue, Any ^c	33.6	16.1
Fatigue, Grade 3 ^c	1.7	0.5
Myalgia, Any ^c	28.9	8.2
Myalgia, Grade 3 ^c	1.4	0.3
Headache, Any ^c	27.2	12.6
Headache, Grade 3 ^c	1.3	0
Arthralgia, Any ^c	18.1	6.4
Arthralgia, Grade 3 ^c	1.3	0.6
Fever, $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}^d$	2.0	0.3
Fever, $>39.0^{\circ}\text{C}/102.2^{\circ}\text{F}^d$	0.1	0.1

N = Exposed set for solicited safety set included all participants with at least 1 documented dose.

^a Placebo was a saline solution.

^b Any grade pain: Defined as any pain neither interfering with nor preventing normal everyday activities (Grade 1), painful when limb is moved and interferes with everyday activities (Grade 2), or significant pain at rest and prevents normal everyday activities (Grade 3).

^c Any grade fatigue, myalgia, headache, arthralgia: Defined as event easily tolerated (Grade 1), interfering with normal activity (Grade 2), or preventing normal activity (Grade 3).

^d Temperature taken by any route (oral, axillary, or tympanic).

In the solicited safety set, the local administration site adverse reactions reported with AREXVY had a median duration of 2 days, and the systemic adverse reactions reported with AREXVY had a median duration ranging between 1 and 2 days.

Unsolicited Adverse Events: In all participants from Study 1, unsolicited adverse events were monitored using paper diary cards during the 30-day period following vaccination (day of vaccination and the next 29 days).

Among participants in the solicited safety set, (AREXVY, n = 879 or placebo, n = 878), unsolicited adverse events occurring within 30 days after vaccination were reported in 14.9% and 14.6% of participants who received AREXVY and placebo, respectively.

In the exposed set, 24,966 participants 60 years of age and older, received at least 1 dose of AREXVY (n = 12,467) or placebo (n = 12,499). Unsolicited adverse events occurring within 30 days of vaccination were reported in 33.0% and 17.8% of participants, respectively. The higher frequency of reported unsolicited adverse events among participants who received AREXVY, compared to participants who received placebo, was primarily attributed to events that are consistent with adverse reactions solicited among participants in the reactogenicity subset. Within 30 days after vaccination, atrial fibrillation was reported in 10 participants who received AREXVY and 4 participants who received placebo (of which 7 events in AREXVY arm and 1 event in placebo arm were serious); the onset of symptoms ranged from 1 to 30 days post vaccination. The currently available information on the atrial fibrillation is insufficient to determine a causal relationship to the vaccine. There were no other notable patterns or numerical imbalances between groups for specific categories of unsolicited adverse events.

(continued on next page)

Serious Adverse Events: In Study 1, participants were monitored for all serious adverse events (SAEs) that occurred during the 6-month period following administration of AREXVY (n = 12,467) or placebo (n = 12,499).

SAEs with onset within 6 months following vaccination were reported at similar rates in participants who received AREXVY (4.2%) or placebo (4.0%). Serious events of atrial fibrillation were reported in 13 participants who received AREXVY and 15 participants who received placebo within 6 months after vaccination.

Deaths: From vaccination through the first analysis of the ongoing Study 1, adverse events leading to death were reported for 49 participants (0.4%) who received AREXVY (n = 12,467) and 58 participants (0.5%) who received placebo (n = 12,499). Based on available information, there is no evidence of causal relationship to AREXVY. Causes of death among participants were consistent with those generally reported in adult and elderly populations.

Potential Immune-Mediated Diseases: In Study 1, participants were monitored for all potential immune-mediated diseases (pIMDs) that occurred during the 6-month period following administration of AREXVY (n = 12,467) or placebo (n = 12,499).

New onset pIMDs or exacerbation of existing pIMDs within 6 months following vaccination were reported for 0.3% of participants who received AREXVY and 0.3% of participants who received placebo. There were no notable imbalances between study groups in individual pIMDs reported.

Serious Adverse Events Reported From Other Studies

Study 2: Guillain-Barré syndrome beginning 9 days after AREXVY vaccination was reported in a participant enrolled in a study site in Japan.

Study 3: Acute disseminated encephalomyelitis was reported in 2 participants enrolled in a study site in South Africa; the onset of the symptoms was 7 and 22 days post vaccination, respectively. One event was fatal and the other non-fatal. These participants received AREXVY concomitantly with FLUARIX QUADRIVALENT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

AREXVY is not approved for use in persons <60 years of age.

In a clinical study that enrolled pregnant individuals who received an investigational unadjuvanted RSV vaccine that contained the same RSVPreF3 antigen as AREXVY, an increase in preterm births was observed compared to pregnant individuals who received placebo (sucrose reconstituted with saline). [see *Use in Specific Populations (8.1) of full prescribing information*].

Data

In a randomized controlled clinical trial that enrolled pregnant individuals in a 2:1 ratio, 3,557 received an investigational unadjuvanted RSV vaccine that contained the same RSVPreF3 antigen as AREXVY and 1,771 received placebo (sucrose reconstituted with saline) at 24 to 34 weeks gestation. In the vaccine and placebo groups, 6.81% and 4.95% of preterm births were reported, respectively.

8.2 Lactation

Risk Summary

It is not known whether AREXVY is excreted in human milk. AREXVY is not approved for use in persons <60 years of age. No human or animal data are available to assess the effects of AREXVY on the breastfed infant or on milk production/excretion. [see *Use in Specific Populations (8.2) of full prescribing information*].

8.4 Pediatric Use

Evidence from an animal model strongly suggests that AREXVY would be unsafe in individuals younger than 2 years of age because of an increased risk of enhanced respiratory disease. Safety and effectiveness in individuals 2 years through 17 years of age have not been established.

8.5 Geriatric Use

AREXVY is approved for use in individuals 60 years of age and older. Of the total number of participants (N = 24,966) who received AREXVY or placebo in Study 1 (NCT04886596), 13,943 (55.8%) were 60 to 69 years of age, 8,978 (36.0%) were 70 to 79 years of age, and 2,045 (8.2%) were 80 years of age and older. [see *Adverse Reactions (6.1), Clinical Studies (14.1) of full prescribing information*].

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients of the potential benefits and risks of vaccination with AREXVY.
- Inform vaccine recipients about the potential for adverse reactions that have been observed following administration of AREXVY.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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helpful prognostic tools and to precision therapies. And already, at institutions like Columbia, genetic discoveries are changing clinical care, driving treatment decisions and spurring family screening.

Thomas Ferkol, MD, whose research focuses on genetic factors that contribute to suppurative airway diseases such as CF and primary ciliary dyskinesia (PCD), similarly regards CF as a road map for genetics research and genetic testing in practice.

"The treatments we're doing now for CF are increasingly based on the genetics of the individual," said Dr. Ferkol, professor and division chief for pediatric pulmonology at the University of North Carolina at Chapel Hill, where the UNC Children's Hospital hosts a rare and genetic lung disease program. For PCD, genetic testing has become a front-line diagnostic tool. But in the future, he hopes, it will also become a determinant for personalized treatment for children with PCD.

The cystic fibrosis transmembrane conductance regulator (CFTR) gene was the first lung disease gene to be discovered using gene-mapping techniques. Since then, and especially in the last 15-20 years, "there's been a lot of progress in the identification of genes for which mutations and variations cause specific forms of pulmonary disease, many of which can now establish a firm diagnosis, and some of which lead to very directed changes in management. There has also been great progress in the availability of genetic testing," said Benjamin A. Raby, MD, MPH, director of the Pulmonary Genetics Center at Brigham and Women's Hospital, Boston, which sees patients with a host of cystic lung diseases, bronchiectatic lung diseases, fibrotic lung diseases, and other conditions, including pulmonary fibrosis and PCD.

Pulmonary fibrosis in adults and PCD in children are two examples of lung diseases for which genetic discoveries have exploded in recent years, with important implications for care now and in the future.

Leveraging genetic testing in PF
PF describes families with two or more members with PF within three degrees of relationship; it is a designation believed to affect 20%-25% of people with PF and occurs predominantly later in the adult years (after

50 years of age), most commonly in autosomal dominant fashion, and amidst a stew of genetic risks, environmental exposures, and other insults.

Dr. Garcia and other researchers have uncovered two main types of genes in which rare variants can give rise to a heritable risk of PF: genes that contribute to the maintenance of telomere length, and genes involved in surfactant metabolism. [Last year, Dr. Garcia and colleagues reported their discovery of both rare and common variants in a "spindle gene," KIF15, in patients with IPF, suggesting an additional pathogenic pathway. The gene controls dynamics of cell division. (*Am J Respir Crit Care Med.* 2022;206[1]:56-69).

Detection of telomere pathway involvement – most commonly involving the TERT gene – is consequential because patients with telomere-associated gene mutations "tend to progress faster and have a more aggressive disease course than patients without these mutations ... regardless of how their scans or biopsies look," as do patients who have short age-adjusted telomere length, said Chad Newton, MD, who directs the Interstitial Lung Disease program at the University of Texas Southwestern in Dallas and researches the genetics of ILD.

Dr. Newton and Dr. Garcia advise patients with PF and a positive family history to undergo panel-based genetic sequencing, along with telomere length measurement. They also advise that undiagnosed first-degree relatives consider what's called "cascade testing" – genetic sequencing for any pathogenic or likely pathogenic rare variants found in the patient's investigation. (Dr. Garcia, who cochairs a National Institutes of Health-funded interstitial lung disease curation panel, said she finds evidence of a pathogenic or likely pathogenic variant in about 25% of patients with a family history of PF.)

"We can use this genetic information to consider starting early [antifibrotic] treatment to try to delay progression ... just as we would with other forms of pulmonary fibrosis," Dr. Newton said, "and to expand our reach to others not sitting in our clinics who have the same rare condition or are at risk."

After cascade testing, Dr. Garcia said, she invites family members with positive results to have baseline

FIBROSIS continued on following page

PULMONARY PERSPECTIVES //

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CT scans and pulmonary function testing. "And if there's anything abnormal, we're inviting them to have regular follow-up testing," she said, "because we advise starting antifibrotic treatment at the very first sign of disease worsening."

Such an approach to genetic testing for patients and relatives is described in a statement commissioned by the Pulmonary Fibrosis Foundation and published last year in the journal *Chest* (2022;162[2]:394-405). The statement, for which Dr. Newton and Dr. Garcia were among the authors, also lists clinical features within patients and families suggestive of a possible genetic pathway, and describes the potential yield for identifying a variant in different clinical scenarios.

Pathogenic variants in telomere genes as well as findings of short telomere length are associated with various extrapulmonary manifestations such as liver dysfunction, bone marrow dysfunction, and head and neck cancers, Dr. Newton said, making surveillance and referrals important. (Rare variants and short telomere length are associated with disease progression across several non-IPF diagnoses as well.)

Moreover, short telomeres may signal the need to avoid long-term immunosuppression. Research published in 2019 from multiple cohorts, and led by Dr. Newton and Dr. Garcia, showed that short telomere length is associated with worse outcomes (faster time to composite death, transplant, FVC decline, and hospitalization) in patients with IPF who received immunosuppression. These adverse outcomes were not found in IPF patients with normal telomere lengths who received similar immunosuppression (*Am J Respir Crit Care Med.* 2019;200[3]:336-347).

Gene sequencing and telomere length measurement are described in the 2020 *Chest* statement on the role of genetic testing in PF as yielding "different yet complementary information." Short age-adjusted telomere length (less than the 10th percentile) is common in those with pathogenic variants in telomere genes, but it can also occur in the absence of identifiable rare telomere-related variants, the statement says. Telomere length testing can be helpful, it notes, in determining the significance of a "variant of unknown significance (VUS)" if gene sequencing identifies one.

The future of genetic screening for PF

Future genetic screening approaches

for PF may cast an even wider net while better stratifying risk for family members. At Brigham and Women's Hospital, where family screening was a major impetus for the 2008 founding of the Pulmonary Genetics Center, research published several years ago by Dr. Raby and his colleagues found that 31% of 107 asymptomatic first-degree relatives of patients with PF had interstitial lung abnormalities on chest CTs – whether or not a family history was reported – and 18% had clear radiographic or physiological manifestations of fibrosis (*Am J Respir Crit Care Med.* 2020;201[10]:1240-8).

"That's more than 10-fold higher than what we thought we'd see, based on prior literature. ... And the numbers were pretty much the same whether or not there was a family history of fibrosis reported by the patient," said Dr. Raby, also the Leila and Irving Perlmutter professor of pediatrics at Harvard Medical School, Boston, and chief of the division of pulmonary medicine at Boston Children's Hospital. "We used to think we only needed to worry about genetic risk when there was a family history. But now we see that sporadic cases are also driven by genetics."

Their study also included a 2-year follow-up chest CT, in which the majority of the screened relatives participated. Of those, 65% who had interstitial changes at baseline showed progression. Four percent of those without interstitial abnormalities at baseline developed abnormalities (*Am J Respir Crit Care Med.* 2023;207[2]:211-4). "The fact that 65% progressed suggests that in the majority of patients what we're finding is something that's real and is going to be clinically meaningful for patients," he said.

Genetic signatures

A next phase of research at Brigham & Women's and Boston Children's, he said, will address PF's "complex genetic signature" and test polygenic risk scores for idiopathic PF that take into account not only rare genetic variants that can be solidly linked to disease but many common genetic variants being detected in genomewide association studies. [By definition, common variants, otherwise known as single-nucleotide polymorphisms (SNPs) occur with greater frequency in the general

population (> 5%), generally reside within noncoding regions, and may contribute to disease risk but alone do not cause disease.]

"As technologies and genetic studies improve, we're seeing we can estimate much better the likelihood of disease than we could 10 years ago," he said. A "potent" common variant called the MUC5B promoter polymorphism has been shown to confer a 3-fold to 20-fold increased risk for PF, he noted. (Polygenic risk scores are also being developed, he said, for asthma and chronic obstructive pulmonary disease.)

"Every time one sees a patient with PF that is thought to be idiopathic one should start thinking about their at-risk family members, particularly their siblings," Dr. Raby said. But in doing so, "wouldn't it be wonderful if we could use polygenic risk scores to assure some [family members] that they're in the lowest tier of risk and might need pulmonary function studies every 5 years, for example, versus someone we'd want to see more frequently, versus someone [for whom] we'd want to start preventive therapy at the earlier signs of declining lung function?"

Moving forward, he and the others said, the field needs more research to determine how genetic risk factors predict disease progression and prospective clinical trials to test whether long-term outcomes are indeed improved by early institution of antifibrotic therapy and other genetics-driven management decisions. "The data we're using to inform prognosis and treatment decisions are compelling, but a lot of it is based on cohort studies and retrospective research," Dr. Newton said.

Multi-institutional transomics studies and other research projects are underway, meanwhile, to build upon gene identifications and learn more about the pathobiology of PF. "We know about two big genetic pathways ... but we need to sort it all out," he said. For instance, "are there intermediate pathways? And where does it actually start? What kind of cell?"

Genetics' impact on PCD

About 20 years ago, only two genes were linked to PCD, a largely autosomal recessive disorder that results from abnormalities in the cilia and subsequently improper airway clearance. Today, said Dr. Ferkol, there are over 50 known genes that, if defective, can lead to PCD.

"Based on our latest estimates, I'd say we can diagnose people using genetics about 70%, maybe 80%, of

the time," Dr. Ferkol said. Genetic testing has become a first-line diagnostic tool for PCD in North America – a significant development given that a definitive diagnosis has long been challenging, he said.

A genetics-based diagnosis of PCD is sometimes challenged by the finding of VUSs on genetic testing (often missense mutations) "because some of the genes involved are huge," noted Dr. Ferkol, who coleads the NIH-funded Genetic Disorders of Mucociliary Clearance Consortium. "But many times, it's straightforward."

Children with PCD have repeated or persistent upper respiratory tract infections beginning early in life – like chronic rhinosinusitis or suppurative otitis media – and chronic bronchitis, leading to bronchiectasis. About half of patients have a spectrum of laterality defects, where organs are malpositioned in a mirror image of normal. Some individuals also have cardiac defects, and subfertility in both males and females can frequently occur.

Just as it has become increasingly clear that CF exists as a continuum, with milder and variant forms having been recognized since the advent of genetic testing, "we're finding genotype-phenotype relationships in PCD," Dr. Ferkol said. "Certain individuals have more rapid pulmonary decline, which is related in part to their genetics."

With PCD, "I'm convinced this is a continuum. Some patients have unmistakable, clear-cut PCD, but I'm sure we're going to find individuals who have milder variants in these PCD-associated genes that lead to milder disease," he said.

There are no specific treatments that will correct cilia dysfunction, and current therapy options are borrowed from other diseases such as asthma and CF. However, newer treatments targeting specific genetic defects are in early clinical studies. Will the gene discoveries and more research open up new avenues for treating PCD, as happened in CF? Dr. Ferkol hopes so.

Approximately 2,000 genetic variants have been identified in the *CFTR* gene, though not all are pathogenic. "The newer, highly effective modulators used in CF target a particular *CFTR* mutation class, so some drugs will work for some people with the disease, but not all," Dr. Ferkol said. "It's personalized medicine."

Modulator therapies designed to correct the malfunctioning proteins

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CHEST

SEPSIS // continued from page 1

throughout the organization.

- Action: Implementing structures and processes to improve the identification, management, and recovery from sepsis.
- Tracking: Measuring sepsis epidemiology, outcomes, and progress toward program goals and the impact of sepsis initiatives.
- Reporting: Providing usable information on sepsis treatment and outcomes to relevant partners.
- Education: Providing sepsis education to health care professionals during onboarding and annually.

Craig Weinert, MD, MPH, a pulmonologist and critical care physician and professor of medicine at the University of Minnesota, Minneapolis, says the point the CDC is making with the announcement is that when these sepsis programs have been implemented at hospitals, they have been successful at reducing mortality. And now, the agency is urging all hospitals to implement them and support them properly.

"It's not asking hospitals to develop new, innovative kinds of sepsis programs. This is not about new drugs or new antibiotics or new devices," Dr. Weinert says. "This is about having hospitals dedicate organizational resources to implementing sepsis programs."

The CDC's announcement is aimed toward hospital administrators, Dr. Weinert adds.

The agency is making the case that sepsis needs more funding in hospitals that either don't have the programs or aren't supporting them with dedicated resources. There's another message as well, Dr. Weinert says.

"COVID basically obliterated sepsis programs for two and a half years," he says. Now the CDC is

See CHEST launches sepsis partnership with CDC, page 16.

saying it's time to divert staff back to sepsis care.

Stepping up sepsis care

Raymund Dantes, MD, assistant professor of medicine at Emory University, Atlanta, one of the developers of the core elements, says this is like a recipe for sepsis care.

Dr. Dantes compares the instructions for hospitals with getting a good restaurant up and running. And in the restaurant business, "you need more than the recipes. You need a leader or manager to ensure you have the right people working together, with the

right supplies, getting the right feedback on their work to continuously improve," he explains.

Dr. Dantes, who is also the physician lead for the Emory Health-care Sepsis Program, says the approach is meant to be flexible to

the size of the hospital, population served, and available resources. He points out that a well-run sepsis program at a 25-bed rural hospital will look very different from the program at a 1,000-bed tertiary care hospital.

Some hospitals, Dr. Dantes says, will be starting from scratch when getting a sepsis program, and for those hospitals, the developers included a "Getting Started" section as part of the detailed, 29-page full report.

In September, Sepsis Awareness Month, the CDC will provide educational information to health care professionals, patients, families, and caregivers about preventing infections that can lead to sepsis through its ongoing Get Ahead of Sepsis campaign. ■

FIBROSIS continued from previous page

made by the CFTR gene have profoundly changed the lives of many with CF, improving lung function and everyday symptoms for patients, allowing them to lead near-normal lives. "It's astonishing," he said.

Dr. Garcia reported consulting for Rejuvenation Technologies and Rejuveron Telomere Therapeutics; in addition, her laboratory has received support from Boehringer Ingelheim and AstraZeneca for investigator-initiated research. Dr. Newton reported he has performed

consulting for Boehringer Ingelheim.

Dr. Ferkol reported involvement in a longitudinal study defining endpoints for future clinical PCD trials funded by ReCode Therapeutics and leadership of an international clinical trial for PCD supported by Parion Sciences. He has received honoraria from the Cystic Fibrosis Foundation and serves as a member of the ReCode Therapeutics PCD Clinical Steering Committee.

Dr. Raby reported no relevant disclosures. ■



BREATHE EASY WHEN DIAGNOSING RESPIRATORY INFECTIONS.

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PIONEERING DIAGNOSTICS

CHEST Advocates raises awareness against tobacco use

BY DREW HARRIS, MD, FCCP

Editor in Chief, CHEST Advocates

"Ew, gross."
"Um, no way."
"Of course not."

Earlier this summer, I partnered with Dr. Melissa Keene, the medical director of a federally qualified health center in southwest Virginia, to talk about tobacco with middle school students. A few minutes after our arrival, it was clear to us that cigarettes weren't cool anymore.

We asked hundreds of kids if they or their friends smoked cigarettes. The above quoted responses were repeated over and over.

Tobacco health advocates have spent decades working on public health messaging surrounding cigarette use, which is clearly working in this Virginian middle school.

But our patients, friends, and family who are already dependent on tobacco products still face addiction, morbidity, and premature mortality. And the ever-changing forms of tobacco delivery pose new challenges

for our collective cessation efforts.

The Summer 2023 issue of *CHEST Advocates* features parents, lawyers, doctors, and nonprofit leaders who all share their inspiring stories of action in the fight against tobacco use.

Learn from tobacco experts, Dr. Susan Waller and Dr. Evan Stepp, about evidence-based approaches to tobacco cessation in young people – including why we should start having conversations by age 11 about smoking or vaping and why it's important to inform youth about big tobacco marketing strategies.

Read an interview with Dr. Anne Melzer, who shares lessons from her career in tobacco advocacy centered in a US veteran population. Dr. Melzer suggests free resources that are available to all clinicians who sometimes struggle to help patients find the best way to quit.

Watch a video of Dr. Iyaad Hasan and Dr. Roy St. John, who run The Breathing Association, a nonprofit in Ohio serving individuals who are

underinsured or uninsured. This organization offers a mobile medical unit that provides a free, evidenced-based program to help with smoking cessation via education, counseling, and personalized quit plans.

Learn from Natasha Phelps, JD, the Director of Equity-Centered Policies at The Center for Black Health & Equity. For more than 2 decades, this organization has focused on building community capacity to give local constituents the tools needed for sustainable health improvements, including tobacco cessation.

Hear from Dr. Panagiotis Behrakis, who – after decades of advocacy against tobacco use – the World Health Organization recognized in May for his Smoke Free Greece program. He explains why his work focuses on a two-pronged approach that places equal emphasis on both cessation and prevention.

Listen to a podcast featuring an amazing organization called Parents Against Vaping e-cigarettes, which

started in response to a predatory marketing strategy by a tobacco company in a school system.

See how CHEST is fighting the battle against smoking and vaping, as told by Dr. Frank Leone, Chair of the Tobacco/Vaping Work Group for the CHEST Health Policy and Advocacy Committee. And, lastly, interact with a timeline of CHEST's advocacy work in tobacco cessation and regulation through the decades.

As Dr. Melzer so eloquently stated in her interview featured in this issue, "tobacco cessation is a process that belongs to everybody, and, therefore, sometimes to nobody." We hope this issue will inspire you to advocate for your patients and partner with your communities in our shared mission to improve education, awareness, and action against tobacco use.

"This article was originally published online on August 25, 2023."



Follow this QR code to explore the complete Summer 2023 issue of *CHEST Advocates*. ■



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CHEST philanthropy: Moving into the future

In an ideal world, change would be progressive, the direction would be clear, and adoption would be easy. We learned in these past few years that sometimes change cannot wait. The vulnerabilities of the health care system were laid bare by the pandemic, including vast disparities in treatment and the urgent need to grow our profession. In the light of these truths, CHEST looked within and asked a difficult question: **Are we doing everything we can?** This question probably sounds very familiar – one you ask every day, one you know the importance of asking. It was time we asked it of ourselves.

Milestones are a good time to reevaluate

Philanthropy is not new to CHEST. We celebrated 25 years of the CHEST Foundation in Nashville during CHEST 2022. Stories about community and clinical research grants were circulated in website blogs, emails, and newsletters and on social media for years. Our committee member volunteers worked hard developing accurate and credible patient education content for the CHEST Foundation website. Because of our faithful donors, communities around the world had access to better medical care and healthier environments.

This is amazing work, but it was time to ask:

- What can CHEST provide that others cannot?
- Where are the gaps we can fill?
- What is our community passionate about changing?

Working collectively, CHEST and CHEST Foundation leadership, along with staff,

rigorously reviewed the success of our past fundraising efforts, areas of commitment our donors had specified, and the direction of interest our membership was leading us toward – like social accountability, growth and diversification of our profession, grassroots community impact, and partnerships to expand our reach. The process took nearly a year to complete – but, in the realm of big changes, that's equal to the time needed for one good, deep breath. Focusing on significant change means narrowing our scope. Meeting these goals would mean changing how we worked and letting go of areas better served elsewhere. CHEST needed to:

1. Align philanthropy with our mission to elevate the value placed on giving, making it a core priority and responsibility of CHEST as an organization.
2. Consolidate philanthropy under CHEST to reduce administrative costs and create efficiencies, allowing more funds to go directly to our philanthropic efforts.
3. Establish clear and transparent areas of giving that resonate with our members as a way to grow our impact and make real change.

With the full support of the CHEST Board of Regents, the CHEST Foundation Board of Advisors – under the guidance of Advisory Chair, Robert De Marco, MD, FCCP, and CHEST Foundation President, Ian Nathanson, MD, FCCP – approved a merger of the CHEST Foundation with CHEST. In order to increase our impact and create greater awareness of CHEST philanthropic efforts, the Board of Advisors got to work

defining a giving strategy that would meet the philanthropic goals and priorities of the CHEST membership. Four areas were defined and are referred to as our philanthropic pillars: clinical research, community impact, support of the profession, and dedication to education. These pillars were approved by the Board of Regents at their spring leadership meeting.

Giving goals without support are just dreams

This transition puts the responsibility for funding the giving pillars in the hands of CHEST. The first step is ensuring the members see the impact of their donations. "When you see your donation in action, you never doubt that you made a good decision," said CHEST CEO, Robert A. Musacchio, PhD. "If we can show that to every member, the next 25 years of CHEST philanthropy are limitless." Helping connect donors to that experience is Meggie Cramer, the new Director of Philanthropy and Advancement, who has experience working directly with health care systems like Rush University Medical Center in Chicago and Hospital Sister Health System in Green Bay, Wisconsin. "When you are giving to programs you are passionate about, you feel good about being a part of making a difference," explained Cramer. "That's my goal – to help our members find areas they care about and know their gift is part of creating real change."

For FAQ about the transition, visit our website via the QR code.



NETWORKS

Sepsis MERCY, 6-min walk test, CPAP overlap, and more...

CRITICAL CARE NETWORK Sepsis/shock section

Now we have MERCY

Beta-lactam antibiotics, including penicillin, carbapenems, and cephalosporins, exhibit time-dependent bacterial eradication. Prolonged infusions are thought to enhance the duration of effective bactericidal antibiotic exposure, decreasing the emergence of drug resistance due to reduced bacterial regrowth between doses – which may lead to cost savings by reducing drug acquisition costs and shortening hospital stays (Lodise TP Jr, et al. *Clin Infect Dis*. 2007;44[3]:357-63).

The best evidence for these benefits comes from observational studies and meta-analyses. The Defining Antibiotic Levels in Intensive Care Unit Patients (DALI) study emphasized the correlation between achieving target concentrations of beta-lactam antibiotics in critically ill patients and positive clinical outcomes for bloodstream infections but not for lung or intra-abdominal

infections (Roberts JA, et al. *Clin Infect Dis*. 2014;58[8]:1072-83). A meta-analysis of 29 studies suggested that prolonged infusion of piperacillin-tazobactam was associated with a mortality benefit compared with intermittent infusions, but prolonged infusions of cephalosporins or carbapenems resulted in comparable outcomes without mortality benefit (Teo J, et al. *Int J Antimicrob Agents*. 2014;43[5]:403-11).

MERCY was a multinational, randomized controlled trial investigating the efficacy of continuous vs intermittent administration of meropenem in critically ill patients with sepsis. The primary outcome, a composite of mortality and emergence of resistant bacteria at day 28, showed no



Dr. Olsen

significant difference between continuous and intermittent administration (47% vs. 49%). Secondary outcomes and adverse events also did not display significant differences, suggesting that continuous meropenem did not improve outcomes compared with intermittent administration (Monti G, et al. *JAMA*. 2023;330[2]:141-51).

MERCY adds to the existing body of evidence suggesting that prolonged and intermittent infusion strategies for meropenem are at least equivalent in efficacy. Therefore, the strategy chosen can depend on other individualized factors.

The views expressed are those of the authors and do not reflect the official policy or position of the U.S. Navy, Department of Defense, or the US Government.

Meredith L. Olsen, MD
Section Member-at-Large
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Section Member-at-Large
Kathryn Pendleton, MD, FCCP,
Section Vice-Chair

DIFFUSE LUNG & TRANSPLANT NETWORK

Pulmonary physiology & rehabilitation section

Use of 6-minute walk distance as a clinical trial outcome in interstitial lung disease

Pulmonary arterial hypertension (PH) and more recently interstitial lung disease (ILD) trials use the 6-minute walk test (6MWT) as a primary outcome due to its ability to conveniently capture a patient's functional capacity and quality of life. However, interpreting the 6MWT in complex and diverse diseases, such as ILD, presents significant challenges.

A recent article (Harari, et al. *Eur Respir Rev*. 2022 Aug 23;31[165]:220087. doi: 10.1183/16000617.0087-2022) advocates for further research to determine the optimal use of the 6MWT as a clinical endpoint in ILD trials. A decline in 6MWT can represent progression of ILD; ILD-related PH;

Networks continued on following page

NETWORKS *continued from previous page*

or musculoskeletal, hematologic, or cardiac etiologies related to the underlying cause of ILD.

To enhance sensitivity, the authors endorse the inclusion of additional parameters in the analysis, possibly as a composite outcome. This would involve integrating the oxygen desaturation profile, dyspnea scores, and heart rate recovery with changes in the 6MWT-distance. They propose this composite measure could serve as a primary endpoint when the study intervention's impact on clinical performance – either improvement or stabilization of ILD or ILD-related PH – is clearly defined. The prognostic significance of these additional parameters in patients with ILD, however, requires further investigation. Inter-test reliability requires a standardized 6MWT, as previously proposed for this population (Lancaster, et al. *Contemporary Clin Trials*. 2021;Nov 25,2020). The standardized test protocol that includes continuous pulse oximetry and heart rate measurement, oxygen titration, and end of test guidelines, will reduce variability and boost reproducibility. In light of recent advancements in the affordability, convenience, and portability of oxygen consumption (VO₂) gas analyzers, we believe that incorporating VO₂ measurements into the 6MWT is a needed incremental improvement. This integration will help define the disease process, its impact on patient performance, and clinical prognosis. Future work should focus on understanding how to effectively estimate VO₂ in combination with a standardized 6MWT to make this test a reliable outcome in trials.

Ruchika Sangani, MD

Section Fellow-in-Training

Saqib Baig, MD

Section Member-at-Large

SLEEP MEDICINE NETWORK

Respiratory-related sleep disorders section

CPAP in overlap syndrome:

Unveiling the evidence

The overlap syndrome (OS), which refers to the co-occurrence of OSA and COPD, was first described by Flenley in 1985

(Flenley DC.

Clin Chest Med.

1985;6[4]:651).

Over the years, numerous studies have demonstrated an increased risk of hospitalization and mortality in patients with



Dr. Gill

OS (Brennan M, et al. 2022;1-10). Despite these findings, limited evidence exists regarding the optimal treatment approach for individuals with OS. CPAP therapy has demonstrated various physiologic advantages for patients with OS (Srivali N, et al. *Sleep Med.*

2023;108:55-60), which contribute to diminished dyspnea symptoms, lowered pro-inflammatory markers, improved arterial blood gases, increased 6-minute walk distance, enhanced FEV₁, and decreased mean pulmonary artery pressure (Suri TM, et al. *FASEB BioAdv.*

2021;3[9]:683-93). CPAP therapy in patients with OS has been linked to a reduction in COPD exacerbations (Voulgaris A, et al. *Clin Respir Jour.* 2023; 17[3]:165), fewer COPD-related hospitalizations (Marin JM, et al. *Am J Respir Crit Care Med.* 2010;182[3]:325-31), decreased

In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

INDICATION

OPSUMIT® (macitentan) is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

WHAT YOU START WITH
CAN CHANGE THE OUTCOME

Create a foundation based on clinical results

Start with OPSUMIT® to reduce the risk of disease progression.¹SERAPHIN trial design and demographics¹⁻³

SERAPHIN was a large (N=742), event-driven, multicenter, long-term (average treatment duration 2 years), randomized, double-blind, placebo-controlled phase 3 trial.

- 36% of patients were not using PAH-specific background therapy at baseline
- 64% were using background therapy with PDE-5 inhibitors or inhaled/oral prostanooids at baseline*
- Patients had predominantly WHO FC II (52%) and FC III (46%) symptoms
- Etiologies included IPAH/HPAH (57%), PAH-CTD (31%), PAH-CHD with repaired shunts (8%), PAH associated with drugs and toxins (3%), and PAH-HIV (1%)
- Mean patient age was 46 years, and 77% of patients were female
- 25% of patients were recently diagnosed (<6 months) and 75% were previously diagnosed (≥6 months)

The primary endpoint in the SERAPHIN trial was time to the first occurrence of death, a significant morbidity event, defined as atrial septostomy, lung transplantation, initiation of IV or SC prostanooids, or clinical worsening of PAH (defined as all of the following: a sustained ≥15% decrease from baseline in 6MWD,[†] worsening of PAH symptoms,[‡] and need for additional PAH treatment) during double-blind treatment plus 7 days.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- Do not administer OPSUMIT® to a pregnant female because it may cause fetal harm.
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.
- For all female patients, OPSUMIT® is available only through a restricted program called the Macitentan Risk Evaluation and Mitigation Strategy (REMS).

Please see additional Important Safety Information on adjacent page.



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macitentan tablets 10 mg

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OPSUMIT® significantly reduced the risk of disease progression by

45% RISK REDUCTION
P<0.0001

HR 0.55; 97.5% CI,
0.39-0.76; *P<0.0001*;
OPSUMIT® 10 mg (n=242),
placebo (n=250)¹

The beneficial effect of OPSUMIT® was primarily attributable to a reduction in clinical worsening events (defined as all of the following: a sustained ≥15% decrease from baseline in 6MWD,[†] worsening of PAH symptoms [a decline in WHO FC], and need for additional PAH treatment).

A primary endpoint event was experienced by 31.4% (n=76) of OPSUMIT®-treated patients vs 46.4% (n=116) of placebo-treated patients.[§] Summary of primary endpoint events (OPSUMIT® vs placebo): worsening PAH (24.4% [n=59] vs 37.2% [n=93]), death (6.6% [n=16] vs 6.8% [n=17]), initiation of IV/SC prostanooids (0.4% [n=1] vs 2.4% [n=6]).

*OPSUMIT® is approved in combination with PDE-5 inhibitors or inhaled prostanooids, but not oral prostanooids.

[†]Confirmed by a second 6-minute walk test performed on a different day within 2 weeks.

[‡]Worsening of PAH included at least one of the following: Advancing to a higher FC from baseline (or no change in WHO FC IV) and signs of right heart failure that does not respond to oral diuretic treatment.

[§]No patients experienced an event of lung transplantation or atrial septostomy in the placebo or OPSUMIT® 10 mg treatment groups.

cardiovascular events (Kendzerska T, et al. *Ann ATS*. 2019;16[1]:71), and an overall decline in mortality rates (Machado ML, et al. *Eur Respir J*. 2010;35[1]:132-7). It is important to acknowledge that, as of now, no randomized clinical trial has specifically addressed the treatment of OS,

leaving recommendations largely reliant on observational studies. Conversely, recent guidelines have proposed the utilization of high-intensity noninvasive ventilation (NIV) for hypercapnic patients with COPD. Thus, extensive research is warranted to characterize distinct sleep-related

breathing disorders within the OS population and to investigate the effects of CPAP in comparison to other NIV modalities on patients with overlap syndrome.

*Solmaz Ehteshami-Afshar, MD
Kirat Gill, MD
Section Member-at-Large*

THORACIC ONCOLOGY & CHEST IMAGING NETWORK

Pleural disease section

Updated pleural disease guidelines from the British Thoracic Society

After more than a decade, the British Thoracic Society (BTS) released updated guidelines for pleural disease

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

Pregnancy: OPSUMIT® may cause fetal harm when administered to a pregnant woman. OPSUMIT® is contraindicated in females who are pregnant. If OPSUMIT® is used during pregnancy, advise the patient of the potential risk to a fetus.

Hypersensitivity: OPSUMIT® is contraindicated in patients with a history of a hypersensitivity reaction to macitentan or any component of the product.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and Macitentan REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT® is available for females only through a restricted program called the Macitentan REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the Macitentan REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Macitentan REMS Program prior to initiating OPSUMIT®. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT®.

Hepatotoxicity

- ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 x ULN was 3.4% for OPSUMIT® vs 4.5% for placebo, and >8 x ULN was 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT® vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT® and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT®. Consider re-initiation of OPSUMIT® when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Fluid Retention

- Peripheral edema and fluid retention are known consequences of PAH and ERAs. In the pivotal PAH study SERAPHIN, edema was reported in 21.9% of the OPSUMIT® group vs 20.5% for placebo.
- Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. In a small study of pulmonary hypertension due to left ventricular dysfunction, more patients in the OPSUMIT® group developed significant fluid retention and had more hospitalizations due to worsening heart failure compared to placebo. Postmarketing cases of edema and fluid retention occurring within weeks of starting OPSUMIT®, some requiring intervention with a diuretic or hospitalization for decompensated heart failure, have been reported.
- Monitor for signs of fluid retention after OPSUMIT® initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause and the possible need to discontinue OPSUMIT®.

Hemoglobin Decrease

- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT®. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT® caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT® group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT® is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT®.

Decreased Sperm Counts

OPSUMIT®, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT® with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT® with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.
- Moderate dual inhibitors of CYP3A4 and CYP2C9 such as fluconazole and amiodarone are predicted to increase macitentan exposure. Avoid concomitant use of OPSUMIT® with moderate dual inhibitors of CYP3A4 and CYP2C9.
- Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with OPSUMIT® should also be avoided.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, for OPSUMIT®, on adjacent pages.

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6MWD=6-minute walk distance; CI=confidence interval; FC=Functional Class; HPAH=heritable PAH; HR=hazard ratio; IPAH=idopathic PAH; IV=intravenous; PAH-CHD=PAH associated with congenital heart disease; PAH-CTD=PAH associated with connective tissue disorders; PAH-HIV=PAH associated with human immunodeficiency virus; PDE-5=phosphodiesterase type 5; SC=subcutaneous; SERAPHIN=Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; WHO=World Health Organization.

References: 1. OPSUMIT® [prescribing information]. Actelion Pharmaceuticals US, Inc. 2. Pulido T, Adzerlikho I, Channick RN, et al; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809-818 and Suppl 1-21. 3. Center for Drug Evaluation and Research, US Food and Drug Administration. OPSUMIT® (macitentan) NDA 204410. Accessed July 19, 2023. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000MedR.pdf



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(Roberts ME, et al. Thorax 2023; 78, s1-s42). Their focus includes spontaneous pneumothorax, undiagnosed unilateral pleural effusion, pleural infections, and malignant pleural effusion (MPE). Separate statements for pleural procedures (Asciak R et al. Thorax. 2023;78:s43-s68) and pleural

mesothelioma (Woolhouse I et al. Thorax. 2018;73:i1-i30) are available. Highlights of the recommendations are:

- Conservative management can be considered for minimally symptomatic primary spontaneous pneumothorax regardless of size. A multi-disciplinary approach and

shared decision-making is vital, especially when deciding between needle aspiration, intercostal drainage or ambulatory devices. Special recommendations were for pregnancy, cystic fibrosis, catamenial, iatrogenic and familial.

- Undiagnosed unilateral pleural

effusion. Besides pleural fluid studies, in those with unclear etiology, thoracoscopic or image-guided pleural biopsy is recommended.

- Pleural infection. Use of renal, age, purulence, infection source, dietary factors (RAPID) scoring may be considered for risk

OPSUMIT® (macitentan) tablets

OPSUMIT® (macitentan) tablets, for oral use

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for OPSUMIT (macitentan). Please review the full Prescribing Information prior to prescribing OPSUMIT.

WARNING: EMBRYO-FETAL TOXICITY

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm [see *Contraindications, Warnings and Precautions, Use in Specific Populations*].
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception [see *Pregnancy Testing in Females of Reproductive Potential (2.2) in Full Prescribing Information, Use in Specific Populations*].
- For all female patients, OPSUMIT is available only through a restricted program called the Macitentan Risk Evaluation and Mitigation Strategy (REMS) [see *Warnings and Precautions*].

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%) [see *Clinical Studies (14.1) in Full Prescribing Information*].

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, advise the patient of the potential risk to a fetus [see *Warnings and Precautions and Use in Specific Populations*].

Hypersensitivity

OPSUMIT is contraindicated in patients with a history of a hypersensitivity reaction to macitentan or any component of the product [see *Adverse Reactions (6.2)*].

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see *Dosage and Administration (2.2) in Full Prescribing Information and Use in Specific Populations*].

OPSUMIT is available for females through the Macitentan REMS Program, a restricted distribution program [see *Warnings and Precautions*].

Macitentan REMS Program

For all females, OPSUMIT is available only through a restricted program called the Macitentan REMS Program, because of the risk of embryo-fetal toxicity [see *Contraindications (4.1), Warnings and Precautions, and Use in Specific Populations*].

Notable requirements of the Macitentan REMS Program include the following:

- Prescribers must be certified with the Macitentan REMS Program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Macitentan REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations*].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.MacitentanREMS.com or 1-888-572-2934. Information on OPSUMIT certified pharmacies or wholesale distributors is available at 1-888-572-2934.

Hepatotoxicity

ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

OPSUMIT® (macitentan) tablets

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 x ULN	3.4%	4.5%
>8 x ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo.

Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated [see *Adverse Reactions*].

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Fluid Retention

Peripheral edema and fluid retention are known clinical consequences of PAH and known effects of ERAs. In the placebo-controlled study of OPSUMIT in PAH, the incidence of edema was 21.9% in the OPSUMIT 10 mg group and 20.5% in the placebo group.

Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. In a small study of OPSUMIT in patients with pulmonary hypertension because of left ventricular dysfunction, more patients in the OPSUMIT group developed significant fluid retention and had more hospitalizations because of worsening heart failure compared to those randomized to placebo. Postmarketing cases of edema and fluid retention occurring within weeks of starting OPSUMIT, some requiring intervention with a diuretic or hospitalization for decompensated heart failure, have been reported [see *Adverse Reactions*].

Monitor for signs of fluid retention after OPSUMIT initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause, such as OPSUMIT or underlying heart failure, and the possible need to discontinue OPSUMIT.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see *Adverse Reactions*].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

OPSUMIT, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility [see *Use in Specific Populations and Nonclinical Toxicology*].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see *Warnings and Precautions*]
- Hepatotoxicity [see *Warnings and Precautions*]
- Fluid Retention [see *Warnings and Precautions*]
- Decrease in Hemoglobin [see *Warnings and Precautions*]

Clinical Trial Experience

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

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study) [see *Clinical Studies (14) in Full Prescribing Information*].

The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

stratification. Drainage of the pleural space with catheter and intrapleural therapy with combination tissue plasminogen activator (TPA) and DNase in residual pleural fluid should be considered. Medical thoracoscopy not supported due to lack of evidence.

- MPE. Definitive pleural intervention based on symptoms and shared decision making was supported. Modality may include talc slurry via chest tube, talc poudrage via thoracoscopy or talc instillation via indwelling pleural catheter. Intrapleural chemotherapy should not be routinely used

for treatment of MPE. These guidelines provide a comprehensive consensus to the literature and reinforce prior recommendations of other professional societies (Gilbert CR et al. *Chest*. 2020;158:2221-8. Miller RJ et al.; *J Bronchology Interv Pulmonol*.

2020;27[4]:229-45. Feller-Kopman DJ et al.; *Am J Respir Crit Care Med*. 2018;198:839-49).

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OPSUMIT® (macitentan) tablets

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2: Adverse Reactions

Adverse Reaction	OPSUMIT 10 mg (N=242) (%)	Placebo (N=249) (%)
Anemia	13	3
Nasopharyngitis/pharyngitis	20	13
Bronchitis	12	6
Headache	14	9
Influenza	6	2
Urinary tract infection	9	6

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OPSUMIT. 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.

Immune system disorders: hypersensitivity reactions (angioedema, pruritus and rash)

Vascular disorders: flushing

Respiratory, thoracic and mediastinal disorders: nasal congestion

Gastrointestinal disorders: Elevations of liver aminotransferases (ALT, AST) and liver injury have been reported with OPSUMIT use; in most cases alternative causes could be identified (heart failure, hepatic congestion, autoimmune hepatitis). Endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure [see Warnings and Precautions].

General disorders and administration site conditions: edema/fluid retention. Cases of edema and fluid retention occurred within weeks of starting OPSUMIT, some requiring intervention with a diuretic, fluid management or hospitalization for decompensated heart failure. [see Warnings and Precautions].

Cardiac disorders: symptomatic hypotension

DRUG INTERACTIONS

Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see Clinical Pharmacology].

Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see Clinical Pharmacology]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology].

Moderate Dual or Combined CYP3A4 and CYP2C9 Inhibitors

Concomitant use of moderate dual inhibitors of CYP3A4 and CYP2C9 such as fluconazole is predicted to increase macitentan exposure approximately 4-fold based on physiologically based pharmacokinetic (PBPK) modelling. Avoid concomitant use of OPSUMIT with moderate dual inhibitors of CYP3A4 and CYP2C9 (such as fluconazole and amiodarone) [see Clinical Pharmacology].

Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with OPSUMIT should also be avoided [see Clinical Pharmacology].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal reproduction studies, OPSUMIT may cause embryo-fetal toxicity, including birth defects and fetal death, when administered to a pregnant female and is contraindicated during pregnancy. There are risks to the mother and the fetus associated with pulmonary arterial hypertension in pregnancy [see Clinical Considerations]. There are limited data on OPSUMIT use in pregnant women. Macitentan was teratogenic in rabbits and rats at all doses tested. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the risk to a fetus [see Contraindications].

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

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

In patients with pulmonary arterial hypertension, pregnancy is associated with an increased rate of maternal and fetal morbidity and mortality, including spontaneous abortion, intrauterine growth restriction and premature labor.

OPSUMIT® (macitentan) tablets

Data

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Lactation

Risk Summary

There are no data on the presence of macitentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for serious adverse reactions in breastfed infants from OPSUMIT advise women not to breastfeed during treatment with OPSUMIT.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPSUMIT, monthly during treatment and one month after stopping treatment with OPSUMIT. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus [see Warnings and Precautions, and Dosage and Administration (2.2) in Full Prescribing Information and Contraindication].

Contraception

Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Warnings and Precautions].

Infertility

Based on findings in animals, OPSUMIT may impair fertility in males of reproductive potential. It is not known whether effects on fertility would be reversible [see Warnings and Precautions, Adverse Reactions and Nonclinical Toxicology].

Pediatric Use

The safety and efficacy of OPSUMIT in children have not been established.

Geriatric Use

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

OVERDOSAGE

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal Impairment

Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Hepatic Impairment

Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

Drug Interactions

In Vitro Studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes. Macitentan is not a substrate or inhibitor of multi-drug resistance protein (P-gp, MDR-1). The active metabolite of macitentan also is not an inhibitor of P-gp/MDR-1 at clinically relevant concentrations.

Macitentan and its active metabolite are not expected to have significant interaction with drug transporters such as organic anion transporting polypeptide (OATP1B1, OATP1B3), multidrug and toxin extrusion protein (MATE-1, MATE-2K), bile salt export pump (BSEP), sodium-taurocholate co-transporting polypeptide (NTCP), organic cation transporter (OCT-1, OCT-3), organic anion transporter (OAT-1, OAT-3) or BCRP transporter at clinically relevant plasma concentrations.

CHEST launches sepsis partnership with the CDC

Earlier this year, CHEST released new clinical resources on sepsis and antibiotic stewardship developed by the Sepsis Resources Steering Committee with grant

support from the US Centers for Disease Control and Prevention (CDC).

The resources – including infographics, videos, podcasts, and

research commentaries – aim to help clinicians increase their knowledge of sepsis prevention and treatment, especially when considering the use of antibiotics.

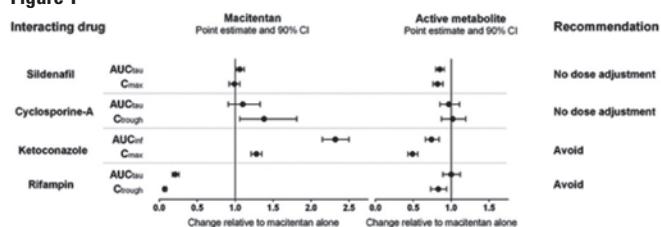
OPSUMIT® (macitentan) tablets

In Vivo Studies

Effect of other drugs on macitentan

The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1



Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see Drug Interactions].

PBPK modeling and simulations based analysis showed that a moderate dual inhibitor of CYP3A4 and CYP2C9 such as fluconazole (400 mg once daily) is predicted to increase macitentan exposure approximately 4-fold without relevant effect on the exposure to its active metabolite [see Drug Interactions].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

Hormonal contraceptives: Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethynodiol diacetate 35 µg).

BCRP Substrate drugs: Macitentan 10 mg once daily did not affect the pharmacokinetics of concomitant use of a BCRP substrate drug (riociguat 1 mg and rosuvastatin 10 mg).

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

Mutagenesis

Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an *in vivo* micronucleus test in rats.

Impairment of Fertility

Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Animal Toxicology

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

PATIENT COUNSELING INFORMATION

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

Manufactured for:

Actelion Pharmaceuticals US, Inc.,
a Janssen Pharmaceutical Company
Titusville, NJ 08560, USA

For patent information: www.janssenpatents.com

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According to CHEST Past President, Steven Q. Simpson, MD, FCCP, who serves as Chair of the Sepsis Resources Steering Committee, sepsis is the number one cause of death in US hospitals. It's also the most expensive condition treated in those hospitals.

"Perhaps the single most important tool we have to fight sepsis is our array of antimicrobial therapies, including antibacterial, antifungal, and antiviral agents," Dr. Simpson said. "It is vital that we use the antibiotics we have wisely and preserve them for future use."

He pointed to the apparent tension between the need to administer broad-spectrum antimicrobials quickly to patients with sepsis

Sepsis is the number one cause of death in US hospitals. It's also the most expensive condition treated in those hospitals.

and the need to limit the use of broad-spectrum agents as much as possible. But these concepts aren't at odds with each other, he said. They're allies in the sepsis war.

CHEST's new resources can help clinicians practice good antimicrobial stewardship as they balance these needs. Included in the collection is a two-part video discussion exploring conservative and aggressive approaches to antibiotic use in suspected sepsis. A series of podcasts delves into complex sepsis cases, and easy-reference infographics outline key components of an antimicrobial stewardship program, rapid diagnostics for infectious diseases in the ICU, and sepsis mimics.

Steering committee members were chosen from CHEST's membership for their clinical expertise in sepsis, infectious diseases, and antimicrobial stewardship. The committee selected topics based on current practice and knowledge gaps where education is most needed.

Working with the CDC increases CHEST's impact in this area. Much of the care of patients with sepsis happens before they reach the ICU. The CDC's broad reach with

SEPSIS continued on following page

This month in the journal CHEST®

Editor's picks

BY PETER J. MAZZONE,
MD, MPH, FCCP

Editor in Chief

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chestnet.org.

Emulating Target Trials Comparing Early and Delayed Intubation Strategies

By Kerollos Nashat Wanis, MD, PhD, et al.

Lower vs Higher Fluid Volumes in Adult Patients With Sepsis – An Updated Systematic Review With Meta-Analysis and Trial Sequential Analysis

By Praleene Sivapalan, MD, et al.

Noninvasive Oxygenation Strategies in Adult Patients With Acute Hypoxic Respiratory Failure: A Systematic Review and Network Meta-Analysis By Tyler Pitre, MD, et al.

The Effectiveness of Flexible Bronchoscopy Simulation-Based Training: A Systematic Review By Eveline C.F. Gerretsen, MSc, et al.

Climate Change for the Pulmonologist: A Focused Review

By Bathmapriya Balakrishnan, BMBS, FCCP, et al.

Addressing Mental Health Needs Among Front-Line Healthcare Workers During the COVID-19 Pandemic By Traci N. Adams, MD, et al.

Lung Transplantation for Pulmonary Arterial Hypertension

By Nicholas A. Kolaitis, MD, MAS.

Observation, Aspiration, or Tube-Thoracostomy for Primary Spontaneous Pneumothorax: A Systematic Review, Meta-Analysis and Cost-Utility Analysis

By Gilgamesh Eamer, MD, et al.

SEPSIS continued from previous page

general and specialty medical audiences allows CHEST to share these resources with a wide array of clinicians who practice inside and outside of the ICU.

"Cooperation with the CDC gives us an opportunity to spread CHEST's knowledge and expertise to a much broader audience, making the CDC a powerful partner and allowing us to serve the nation and beyond in a way that we cannot do by ourselves," Dr. Simpson said. ■



Access the full collection of sepsis resources at chestnet.org/topic-collections/sepsis

PULMONARY PERSPECTIVES®

Home oxygen therapy: What do the data show?

BY CHARLES F. KREISEL, MD, AND RAJIV SONTI, MD

Inhalers, nebulizers, antibiotics, and steroids – these are some of the most common tools in our pulmonary arsenal that we deploy on a daily basis. But, there is no treatment more fundamental to a pulmonary practitioner than oxygen. So how is it that something that naturally occurs and comprises 21% of ambient air has become so medicalized?

It is difficult (perhaps impossible) to find a pulmonologist or a hospitalist who has not included the phrase "obtain ambulatory saturation to qualify the patient for home oxygen" in at least one of their progress notes on a daily basis. Chronic obstructive pulmonary disease (COPD) is the most common reason for the prescription of long-term oxygen therapy (LTOT), a large industry tightly regulated by the Centers for Medicare & Medicaid Services (CMS).

The evidence for the use of LTOT in patients with COPD dates back to two seminal papers published in 1980 and 1981. The British Medical Research Council Working Party conducted the BMRC trial, in which 87 patients with a PaO_2 of 40 mm Hg to 60 mm Hg, CO_2 retention, and a history of congestive heart failure were randomized to treatment with 15 hours per day of home oxygen therapy, starting at 2 L and titrating to PaO_2 of 60 mm Hg vs. standard therapy without oxygen (*Lancet*. 1981;1[8222]:681-6). There was an impressive 22% mortality benefit at 3 years.

Another study published around the same time, the Continuous or Nocturnal Oxygen Therapy in Hypoxic Chronic Obstructive Lung Disease (NOTT) trial (*Ann Intern Med*. 1980;93[3]:391-8) directly compared continuous 24-hour to nocturnal home oxygen therapy in patients with COPD and severe hypoxemia with a PaO_2 less than 55 mm Hg. Again, there was an impressive mortality benefit in favor of continuous home oxygen with a 9% and 18% mortality difference at 1 and 2 years of enrollment, respectively.

Afterward, it became universally accepted dogma that patients with COPD and severe hypoxemia stood to substantially benefit from LTOT. For years, it was the only therapy associated with a mortality reduction. The LOTT study (Albert RK, et al. *N Engl J Med*. 2016;375[17]:1617-27) included 768 patients with stable COPD and a resting or nocturnal SpO_2 of 89% to 93%, as well as patients with moderate exercise-induced desaturation (SpO_2 of greater than or equal to 80% and less than 90% for greater than or equal to 10 seconds

during the 6-minute walk test). Half of these patients received oxygen for 24 hours per day, during sleep, or during exercise (depending on when desaturation would occur) and half received no oxygen. There was no difference in time to death or first hospitalization or in rates of hospitalization or exacerbation. There was also no difference between groups in quality of life, lung function, or distance walked in 6 minutes.

The INOX (Lacasse Y, et al. *N Engl J Med*. 2020;383[12]:1129-38) trial, in which 243 patients with oxygen saturation less than 90% for at least 30% of the night were assigned to receive nocturnal vs sham oxygen, found similar results. There was no difference in the composite outcome of all-cause mortality and progression to 24-7 oxygen requirement (according to the criteria originally defined by NOTT). A 2022 systematic review and

meta-analysis including six studies designed to assess the role of LTOT in patients with COPD and moderate desaturation, including LOTT and INOX, found no benefit to providing LTOT (Lacasse Y, et al. *Lancet Respir Med*. 2022;10[11]:1029-37).

Based on these studies, a resting SpO_2 of 88% seems to be the threshold below which LTOT improves outcomes. CMS lists four classes of patients eligible for LTOT: (1) Patients with PaO_2 < 55 mm Hg or pulse oximetry less than or equal to 88% at rest or (2) during sleep or (3) during exercise, and (4) patients with PaO_2 > 55 mm Hg but less than or equal to 59 mm Hg or pulse oximetry of 89% who have lower extremity edema, evidence of pulmonary hypertension, or erythrocythemia (Centers for Medicare & Medicaid Services. Medicare Coverage Database. 2021;100-103:240.2 (<https://tinyurl.com/2p9fv4ad>)). These criteria reflect the inclusion criteria of the BMRC trial and NOTT.

COPD management has changed significantly in the 40 years since NOTT was published. In the early 1980s, standard of care included an inhaled beta-agonist and oral theophylline. We now prescribe a regimen of modern-day inhaler combinations, which can lead to a mortality benefit in the correct population. Additionally, rates of smoking are markedly lower now than they were in 1980. In the Minnesota Heart Survey, the prevalence of being an ever-smoking man or woman in 1980 compared with 2009 dropped from 71.6% and 54.7% to 44.2% and 39.6%, respectively (Filion KB, et al. *Am J Public Health*. 2012;102[4]:705-13). Treatment of common comorbid conditions has also dramatically improved.

OXYGEN continued on page 20



SABA, short-acting β_2 -agonist.

Reference: 1. Larsson K, Kankaanranta H, Janson C, et al. Bringing asthma care into the twenty-first century. *NPJ Prim Care Respir Med.* 2020;30(1):25.

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Highlights of calendar year 2024 Medicare Physician Fee Schedule proposed rule

BY HUMAYUN ANJUM, MD,

FCCP

CHEST Physician Editorial Board Member

The proposed Medicare Physician Fee Schedule for CY 2024 was published by the Centers for Medicare & Medicaid Services (CMS) in July 2023. Physicians who specialize in pulmonary, critical care, and sleep medicine will be impacted by a number of policy and payment changes. Additionally, keep in mind that this is the proposed rule and CMS will publish the final rule in November. Following are some of the key points for our readers:

1 The conversion factor that CMS is suggesting for 2024 is \$32.75, which represents a \$1.14 (-3.34%) reduction. The current conversion factor is \$33.89. This is due to the requirement that Medicare spending must remain budget neutral by statute.

2 The forecast is that pulmonary specialists will experience an

estimated 1.09% reduction in overall Medicare reimbursements if the proposed changes are approved. Medicare reimbursements for critical care specialists will be reduced by 2.51%, and sleep medicine specialists will be seeing a 0.75% increase.

3 Interestingly, CMS is proposing a Healthcare Common Procedure Coding System (HCPCS) code G2211 that will have a distinct add-on payment starting on January 1, 2024. This add-on code is meant to more accurately recognize the resource costs of evaluation and management visits for primary care and treatment of patients with complex chronic medical conditions. Payment for this add-on code would have a redistributive impact on all other CY 2024 payments that is lower than what was predicted for this policy in CY 2021 Medicare Physician Fee Schedule, which was not implemented at the request of various surgical specialties.

4 Split (or shared) E/M visits in hospitals and other institutional settings are those that are provided in part by doctors and in part by non-physician practitioners of the same specialty but billed under a single provider. Thankfully, CMS is recommending a delay in the definition of the "substantive portion" of a visit as more than 50% of the total time spent until at least December 31, 2024. Instead, they are going to keep the current definition of the "substantive portion" for CY 2024, which permits use of either more than half of the visit's total time or performance of one of the three major components (history, exam, or MDM) to determine who bills for the visit. Please remember that Critical Care services (99291/99292) may also be shared or split; however, in this case, billing is based only on time.

5 According to CMS's current regulatory stance, teaching physicians have to be physically present to charge for services involving residents at the end of the COVID-19 Public Health Emergency. Congress,

CHEST and the American Thoracic Society sent joint comments to the Centers for Medicare & Medicaid Services regarding the MPFS Proposed Rule. Read the letter at chestnet.org/advocacy.

on the other hand, stepped in and passed legislation to expand Medicare coverage of a number of telehealth services. In accordance with the expanded telehealth policies adopted by Congress, CMS is recommending that teaching physicians be permitted to employ audio/video real-time communications technology when supervising a resident physician providing telehealth services to Medicare beneficiaries for CY 2024.

Reviewed by Mike Nelson, MD, FCCP, Chair of the Health Policy and Advocacy Committee

The CMS's document is comprehensive, so please visit this link for more information (<https://tinyurl.com/mrnxkkbw>). ■



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OXYGEN continued from page 17

A report containing all fee-for-service data published in 2021 by CMS reported oxygen therapy accounted for 9.8% of all DME costs covered by CMS and totaled approximately \$800,000,000 (Centers for Medicare & Medicaid Services. FFS Data. 2021 (<https://tinyurl.com/38p8da2c>). This represents a significant financial burden to our health system and government.

Two of the eligible groups per CMS (those with isolated ambulatory or nocturnal hypoxemia) do not benefit from LTOT in RCTs. The other two groups are eligible based on trial data from a small number of patients who were studied more than 40 years ago. These facts raise serious questions about the cost-efficacy of LTOT.

So where does this leave us?

There are significant barriers to repeating large randomized oxygen trials. Due to broad inclusion criteria for LTOT by CMS, there are undoubtedly many people prescribed LTOT for whom there is minimal to no benefit. Patients often feel restricted in their mobility

and may feel isolated being tethered to medical equipment. It is good practice to think about LTOT the same way we do any other therapy we provide - as a medicine with associated risks, benefits, and costs.

Despite its ubiquity, oxygen remains an important therapeutic tool. Still, choosing wisely means recognizing that not all patients who qualify for LTOT by CMS criteria will benefit. ■

Drs. Kreisel and Sonti are with the Division of Pulmonary, Critical Care, and Sleep Medicine, MedStar Georgetown University Hospital, Washington, DC.

In memoriam

CHEST has been informed of the following deaths of CHEST members. We remember our colleagues and extend our sincere condolences.

Albert L. Waldo, MD, FCCP
Tyrus Schroeder, MD, FCCP

Rome classification of exacerbation predicts prognosis

BY HEIDI SPLETE

FROM THE JOURNAL CHEST®

Adults with exacerbations of chronic obstructive pulmonary disease (ECOPD) whose condition was classified as severe using the Rome criteria had a higher risk of death at 1 year than those who were classified as having moderate or mild disease, as determined from data from more than 300 individuals.

Patients hospitalized with severe exacerbations of ECOPD are at increased risk for worse clinical outcomes and death, so early identification is important, according to Ernesto Crisafulli, MD, of the University of Verona (Italy) and Azienda Ospedaliera Universitaria Integrata of Verona, and colleagues.

To help predict prognosis for patients with ECOPD, an expert opinion group updated the definition of ECOPD using a new severity classification known as the Rome definition, which grades ECOPD as mild, moderate, or severe on the basis of more objective and disease-related aspects.

However, data on the clinical usefulness of the Rome criteria are limited.

In a study published in the journal *Chest* (2023 Jul 26. doi: 10.1016/j.chest.2023.07.021), the researchers retrospectively categorized 347 adults hospitalized with ECOPD using the Rome severity classifications of mild, moderate, and severe.

Classifications were made using baseline, clinical, and microbiological factors, as well as gas analysis and laboratory variables.

The researchers also reviewed data on the length of hospital stay and mortality (in-hospital and over a follow-up of 6 months to 3 years).

Approximately one-third of the patients (39%) studied were classified as having mild disease, 31% as having moderate disease, and 30% as having severe illness. Overall,

hospital stay was significantly longer for those patients who had severe disease, although in-hospital mortality was similar across all three groups.

Patients classified as having severe disease also had a worse prognosis at all follow-up time points, and severe classification was significantly associated with worse cumulative survival at 1 year and 3 years (Gehan-Breslow-Wilson test, $P = .032$ and $P = .004$, respectively).

In a multivariate analysis, the risk of death at 1 year was found to be significantly higher among patients classified as severe or moderate (hazard ratio, 1.99 and 1.47, respectively), compared with those classified as mild.

Mortality risk also was higher among patients who were aged 80 years and older and among those patients requiring long-term oxygen therapy or who had a history of ECOPD episodes, the researchers noted. In contrast, body mass index in the range of 25–29 kg/m² was found to be associated with lower risk.

The study was limited by several factors, including the replacement of dyspnea perception in the Rome classification with other objective measures, according to the researchers.

Other limitations include the retrospective design, small sample size, use of data from a single center, and lack of data on causes of mortality. Women were underrepresented in the study, and so additional research involving women is needed.

The results suggest that the Rome classification allows for the effective identification of patients with ECOPD who have a worse prognosis. The Rome classification may help guide disease management through targeted interventions and personalized care programs for this population, the researchers concluded.

The study received no outside funding. The researchers disclosed no relevant financial relationships. ■

Patients classified as having severe disease also had a worse prognosis at all follow-up points and severe classification was significantly associated with worse cumulative survival.



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Sotatercept linked to disease modification in pulmonary arterial hypertension

BY ELENA RIBOLDI, PHARM.D,
PHD

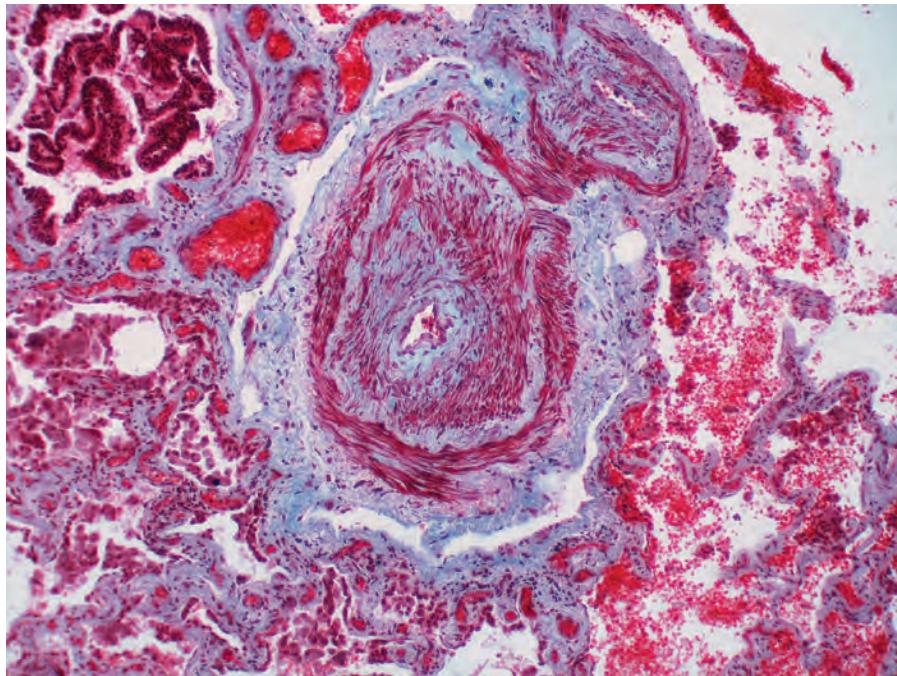
MILAN – Sotatercept, a first-in-class activin-signaling inhibitor, is currently under scrutiny as a potential game-changer in the treatment of pulmonary arterial hypertension (PAH). Data unveiled at the 2023 European Respiratory Society International Congress suggest that sotatercept treatment has the capacity to deliver significant clinical benefits and could reshape the trajectory of this challenging disease. Experts are cautiously optimistic that this drug may soon find a place within the PAH treatment algorithm.

The STELLAR trial: A milestone in PAH research

PAH is intricately linked to the dysregulation of members within the TGF-beta superfamily, including activin receptor type IIA (ActRIIA) and its ligands activin A and activin B. This signaling pathway is believed to be a driving force behind the pulmonary vascular remodeling observed in PAH patients. Sotatercept, a fusion protein acting as a ligand trap for selected TGF-beta superfamily members, has been proposed to recalibrate pulmonary vascular homeostasis by promoting growth-inhibiting and pro-apoptotic signaling.

Sotatercept was tested first in a phase 2 trial (PULSAR) and later in a phase 3 trial (STELLAR). The STELLAR clinical trial, funded by Acceleron Pharma (now a subsidiary of Merck), was the subject of two presentations given by Marius M. Hoeper, MD, director of the department of respiratory medicine at Hannover Medical School, Hannover, Germany.

Dr. Hoeper commented on results published in the New England Journal of Medicine (2023 Apr 20. doi: 10.1056/NEJMoa2213558) during a session titled, "Disease Modification in Pulmonary Arterial Hypertension." Later, during the "From the Editor's Desk" session, he presented new results recently published in the European Respiratory Journal (2023. doi: 10.1183/13993003.01107-2023) about the effects of sotatercept



This pulmonary artery shows marked intimal thickening and adventitial thickening. The red-staining cells in the intima are probably myofibroblasts.

on hemodynamics and right heart function.

Disease modification in PAH

In his initial address, Dr. Hoeper expounded on the concept of reverse remodeling as a therapeutic avenue for PAH. "PAH is not a disease of pulmonary vasoconstriction," he clarified, "but a disease of proliferation. Endothelial cells and pulmonary vascular muscle cells proliferate and obliterate the lumen.

Sotatercept, a fusion protein acting as a ligand trap for TGF-beta, has been proposed to recalibrate pulmonary vascular homeostasis by promoting growth-inhibiting and pro-apoptotic signaling.

It has been hypothesized that, when we target this system successfully, we may not only stop disease progression, but we may have a chance to have at least some reverse remodeling, because, if these cells go into apoptosis, there may be a partial reopening of the vessels."

"Sotatercept is probably going to be a game-changer in our field," Dr. Hoeper continued. "Is sotatercept a disease-modifying agent? It certainly induces disease improvement; in a few patients, although not in the majority, we see a normalization of hemodynamics. We target the underlying pathophysiology; this is clearly distinct from symptomatic treatment." Dr. Hoeper went through the list of characteristics that a disease-modifying agent should have.

"To be able to say that a drug endures sustained clinical benefit, according to the FDA, you need to withdraw the drug, and this is something we do not know. We know that we can interrupt the treatment once or twice, but long term I do not believe that," he said, while acknowledging the need for more extended-term safety and efficacy data.

Unmasking hemodynamic impact

Dr. Hoeper's second presentation focused on a post hoc analysis of the STELLAR trial never presented before. He analyzed right heart catheterization (RHC) and echocardiography (ECHO) data. With sotatercept treatment at week 24, the researchers observed:

- A small increase in systemic blood pressure and systemic vascular resistance.
- No changes in systolic and diastolic volumes of the left ventricle.
- A small but significant reduction in left ventricular ejection fraction.
- A great reduction in the mean pulmonary artery pressure (mPAP).
- No change in cardiac output.
- An improvement in pulmonary artery compliance.
- A reduction in the right ventricle work and in right atrial pressure.
- An improvement of echocardiographic parameters, including a significant decrease in tricuspid regurgitation.

"A drop of roughly 14 mm Hg

in mPAP is something that we have never seen in PAH with any other add-on medication. This was entirely driven by improvement in the sotatercept group, not by deterioration in the placebo group," Dr. Hoeper pointed out. Of note, change in mPAP correlated with changes in NT-proBNP and with changes in 6-minute walk distance (6MWD), the primary endpoint of the STELLAR trial. "We effectively unload the right ventricle by lowering the artery pressure. What we observe is exactly what we want to achieve in patients with PAH, because the heart is what really matters," he concluded.

A new course in PAH treatment?

Olivier Sitbon, MD, PhD, professor of respiratory medicine at Université Paris-Saclay and consultant at the French Referral Center for Pulmonary Hypertension, echoed Dr. Hoeper's enthusiasm. "What is important about sotatercept studies is that for the first time it has been demonstrated that to add a fourth drug improves hemodynamics in PAH patients on background triple-combination therapy. Today, triple therapy is the maximum treatment before lung transplantation," he told this news organization.

Dr. Sitbon highlighted ongoing studies with sotatercept, including the ZENITH trial, focused on high-risk PAH patients, and the HYPERION trial, aimed at patients diagnosed within the first year of their PAH journey. He acknowledged that experts currently lack consensus on the ideal position for sotatercept within the PAH treatment algorithm. However, he anticipates a lively debate and expects sotatercept to find its place as a second-line treatment for intermediate low-risk or intermediate high-risk patients, with potential consideration for high-risk patients.

"There are two more studies ongoing with sotatercept: the ZENITH trial, dedicated to PAH patients at high risk, whose primary endpoint is mortality/need for lung transplant, and the HYPERION trial, dedicated to patients diagnosed less than 1 year (not really newly diagnosed but quite incident, while patients included in previous trial were very prevalent), whose primary endpoint is time to clinical

SOTATERCEPT continued on following page

Long COVID tied to greater long-term health risks

BY JAY CROFT

People who have been infected with the COVID-19 virus have a greater risk of many long-term health conditions, including diabetes, lung problems, fatigue, blood clots, and disorders affecting the gastrointestinal and musculoskeletal systems.

That is the finding of a new study from Washington University in St. Louis. The school distributed a press release about the study, which was published in the journal *Nature Medicine* (2023 Aug 21. doi: 10.1038/s41591-023-02521-2).

"Some estimates show more than 90% of the U.S. population has been infected with COVID-19," Ziyad Al-Aly, chief of research

and development at Veterans Affairs St. Louis Health Care System and clinical epidemiologist at Washington University, told the St. Louis Post-Dispatch.

"Doctors need to realize that their patients could be at risk of these conditions, be it heart disease or lung problems or brain problems – they're at risk."

The researchers compared the health records for 138,000 patients who had been infected with those of 6 million who had not. They followed 80 health conditions associated with long COVID for 2 years. They used unnamed records from the VA.

"There was really nothing at all looking at what happens to people at 2 years after the infection," Dr. Al-Aly said. "So we decided to take a look."

Patients who hadn't been hospitalized within 30 days of infection had a higher risk of death 6 months after recovery, and a higher risk of hospitalization within 18 months.

They had higher risk of diabetes, fatigue, joint pain, and other problems compared with people who had not been infected.

"In the nonhospitalized group, risks remained elevated for several problems, for several organ systems," Dr. Al-Aly said. "For the people who were hospitalized, the risk was ubiquitous across all organ systems. It really spans the gamut with respect to the organ systems that are affected."

People who had been hospitalized had a 65% greater risk of illnesses after 2 years. Nonhospitalized patients had just a 35% greater risk. ■

SOTATERCEPT *continued from previous page*

worsening," Dr. Sitbon noted, pointing out that there is currently no consensus among the experts about where to place sotatercept in the PAH treatment algorithm.

Further insights into sotatercept

The ERS Congress also unveiled two additional studies that provided fresh perspectives on sotatercept's potential. Ioana R. Preston, MD, from Tufts Medical Center in Boston, presented the first interim analysis of SOTERIA, a long-term follow-up study involving 409 patients with a median exposure duration of 462 days to sotatercept. Treatment-emergent adverse events (TEAEs) were reported by 80% of patients, with 20% reporting a serious TEAE. Overall, four serious TEAEs (1% of patients) led to death, but only five patients (1.2%) discontinued sotatercept because of TEAE.

Notably, improvements in clinical efficacy measures persisted after 1 year. During SOTERIA, roughly 3% of patients on any prostacyclin discontinued it. "Results of SOTERIA support the long-term durable clinical benefit and safety of sotatercept for the treatment of PAH. Of note, patients were offered home

self-administration therapy, so they do not need to come back to the office," Dr. Preston said.

A second late-breaking abstract presented by Vallerie McLaughlin, MD, University of Michigan, Ann Arbor, described the possible long-term impact of sotatercept on morbidity and mortality. The STELLAR trial data were analyzed to see how the risk profile of patients changed in the 24 weeks of study. Real-world registry data from the COMPERA registry were then used to extrapolate mortality and transplant need over 30 years based on risk transition.

According to the simulation model, adding sotatercept to background therapy is expected to increase life expectancy by threefold, while avoiding nearly 700 hospitalizations and four lung/heart-lung transplants per 1,000 patients. "Real-world data are needed to confirm these findings," cautioned Dr. McLaughlin.

Dr. Hoeper disclosed speaking and consulting fees from Acceleron, Actelion, Altavant, AOP Health, Bayer, Ferrer, Janssen, Keros, and MSD. Dr. Sitbon disclosed speaking and consulting fees from Acceleron Pharmaceuticals, Altavant Sciences,

AOP Orphan, Bayer, Ferrer, Gossamer Bio, Janssen, MSD, and United Therapeutics, and grant/research support from Acceleron Pharmaceuticals, AOP Orphan, Bayer, Janssen, and MSD.

Dr. Preston disclosed speaking and consulting fees from Janssen and United Therapeutics, and grant/research support from Janssen and Respira Therapeutics. She has participated in scientific advisory boards for Aereovate, Altavant, and

Gossamer Bio, and was in the Steering Committee of Acceleron, Liquidia, and United Therapeutics. Dr. McLaughlin has received speaking and consulting fees from Aerami, Aereovate, Caremark, Corvista, Enzyvant, Gossamer Bio, Janssen, Merck, United Therapeutics, and Vertex, and grant/research support from Aerovate, Enzyvant, Gossamer Bio, Janssen, Merck, and Sonovia. She is a member of the Board of Directors of Clene. ■

"Results of SOTERIA support the long-term durable clinical benefit and safety of sotatercept for the treatment of PAH."

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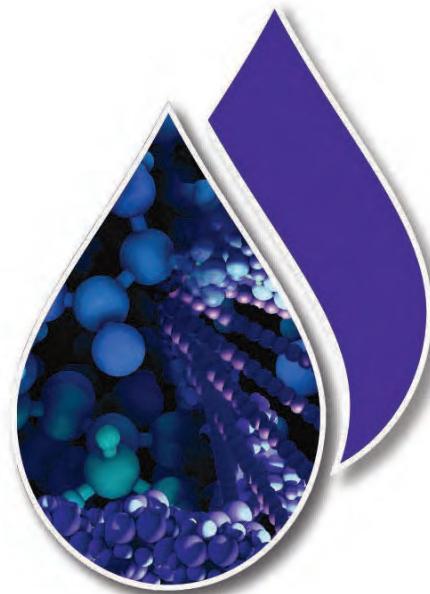
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