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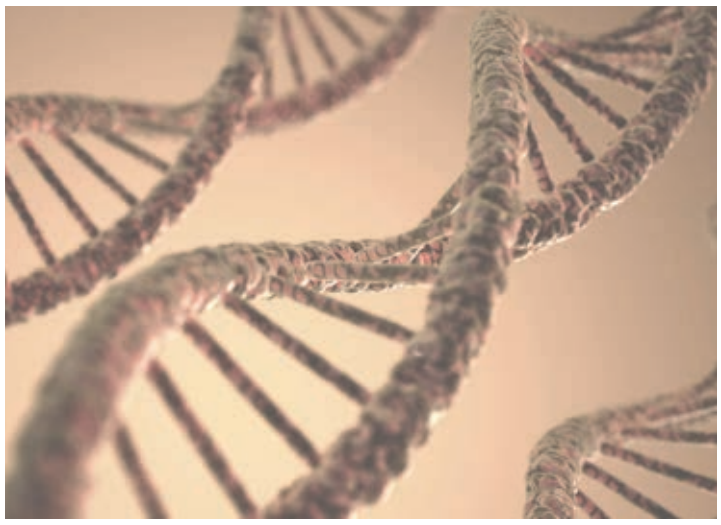

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In the COPDGene study, 55% of smokers who did not meet spirometric criteria for COPD had respiratory disease.

COPD-like symptoms in GOLD 0 patients

BY MIKE BOCK
Frontline Medical News

More than half of smokers with normal spirometry had some form of respiratory-related impairment associated with COPD, Dr. Elizabeth A. Regan and the Genetic Epidemiology of COPD (COPDGene) investigators reported in JAMA Internal Medicine.

The findings imply that up to 35 million current and former smokers older than age 55 years in the United States may have some form of respiratory-related impairment associated with COPD that has gone undiagnosed with standard spirometry, the researchers wrote (JAMA Internal Med. 2015 June 22 (doi:10.1001/jamainternmed.2015.2735).

The researchers found that 55% of current and former smokers older than age 55 years in the study who did not meet the spirometric criteria for COPD (GOLD [Global Initiative for Chronic Obstructive Lung Disease] 0 score) had significant respiratory disease.

Their conclusion was based on seven metrics: chronic bronchitis (seen in 12.6% of the GOLD 0 participants), history of severe respiratory exacerbations (seen in 4.3%), dyspnea score of at least 2 (seen in 23.5%), quantitative emphysema exceeding 5% (seen in 9.8%), quantitative gas trap-

See **GOLD 0** • *page 9*

Idarucizumab flips the effects of dabigatran

Novel drug reverses anticoagulation.

BY TED BOSWORTH
Frontline Medical News

TORONTO – Idarucizumab quickly and safely reverses the anticoagulant effects of dabigatran, whether the goal is to control serious bleeding or to permit urgent surgery, based on interim results of a multicenter trial.

Idarucizumab is a monoclonal antibody that binds to dabigatran to reverse its activity. The data, presented by Dr. V. Charles Pollack Jr. at the International Society on Thrombosis and Haemostasis congress, involved the first 90 patients of an ongoing trial with a planned enrollment of 300. The data from this trial, called REVERSE-AD, were published online simultaneously with its presentation at the congress (N. Engl. J. Med 2015 [doi:10.1056/NEJMoa1502000]).

"Non–vitamin K antagonist oral anticoagulants (NOACs) are generally safer than warfarin, and provide similar or improved efficacy in the prevention of stroke in patients with nonvalvular atrial fibrillation and in the prevention and treatment of venous thromboembolism," Dr. Pollack said in an interview. "Nonetheless, serious bleeding events may occur

See **Idarucizumab** • *page 8*

INSIDE

OSA gets missed in cardiac patients

BY SHARON WORCESTER
Frontline Medical News

DENVER – Obstructive sleep apnea was common among patients in the multinational Sleep and Stent Study who underwent successful percutaneous coronary intervention, but most of those affected had no daytime sleepiness, and only about half had positive findings on the Berlin Questionnaire.

Further, findings at up to 4 years of follow-up show that coronary artery disease patients with vs. without obstructive sleep apnea (OSA) had nearly twice the risk of adverse events.

The findings suggest that OSA has important clinical implications for coronary artery disease (CAD), and that validated tools for identifying OSA risk in the general population may not be useful in those with cardiovascular disease, Sofia Furlan, Ph.D. said in a press briefing at an international

See **Sleep and Stent Study** • *page 10*

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

HELP HER WRITE FUTURE CHAPTERS

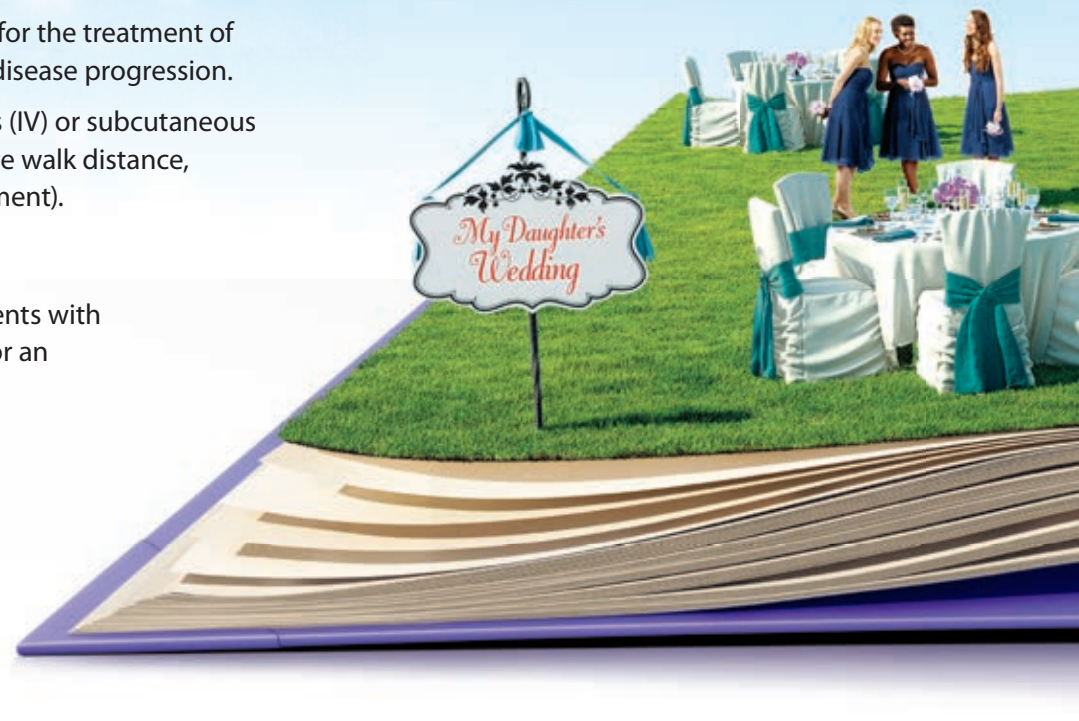
OPSUMIT® (macitentan) is the only ERA approved to delay disease progression as both monotherapy and in combination with PDE-5 inhibitors or inhaled prostanoids[1]

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

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced 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 were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
- 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%).



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 OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).**

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, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT 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 OPSUMIT 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 OPSUMIT 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.

6MWD: 6-minute walk distance; ERA: endothelin receptor antagonist; IV: intravenous; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase type 5; SC: subcutaneous; SERAPHIN: **S**tudy with an **E**ndothelin **R**eceptor **A**ntagonist in **P**ulmonary Arterial **H**ypertension to **I**mprove Cli**N**ical Outcome; ULN: upper limit of normal; WHO: World Health Organization.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

Patient dramatization

SERAPHIN: The first long-term outcome trial in PAH (average treatment 2 years) to demonstrate the use of both monotherapy and combination therapy to delay disease progression[1,2]

Patients were treated with OPSUMIT monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

- SERAPHIN included both incident (recently diagnosed) and prevalent (previously diagnosed) patients[3]
- Overall, the median time from diagnosis was 15 months, ranging from 1 day to 36 years[3]
- 25% of patients were diagnosed less than 6 months prior to enrollment in the study[3]

SERAPHIN was a randomized, double-blind, placebo-controlled, event-driven outcome study to assess the effect of OPSUMIT on disease progression (time to first significant morbidity or mortality event), as defined by death, atrial septostomy, lung transplantation, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).[1,2]

WARNINGS AND PRECAUTIONS (continued)

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN was 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × 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 × 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.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

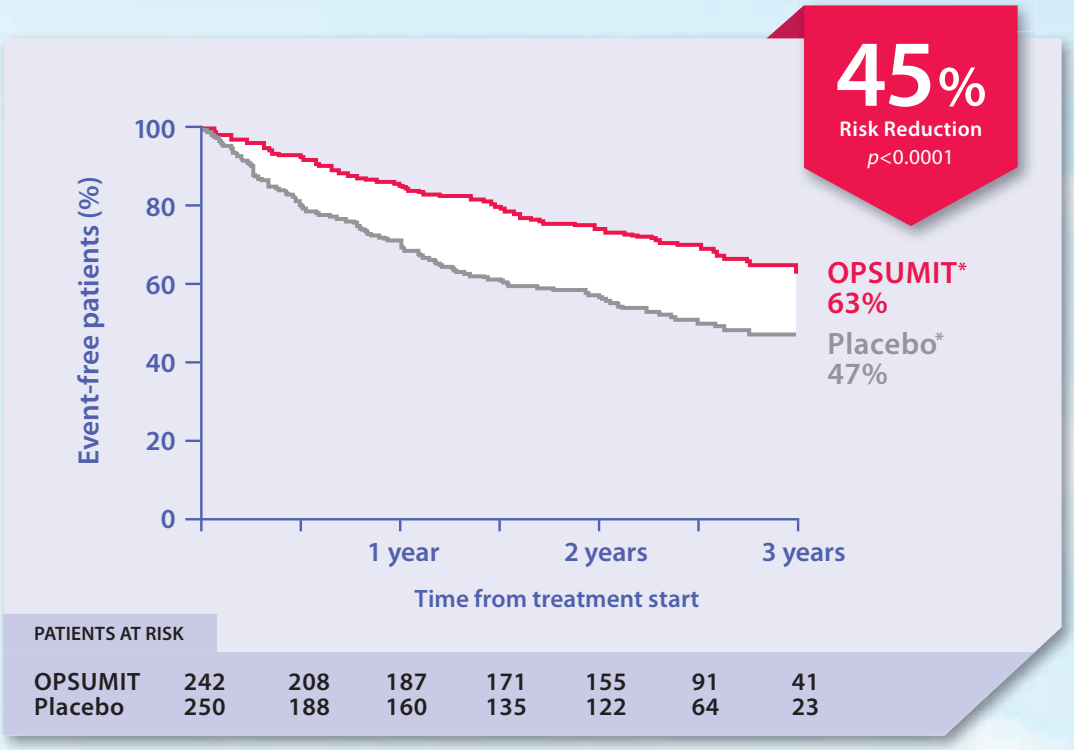
FUTURE. FORWARD. | Opsumit®
macitentan tablets 10 mg

INDICATION

OPSUMIT® (macitentan) is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

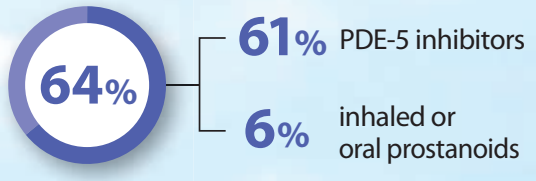
Keep disease progression in mind from the start of therapy: OPSUMIT is the only ERA approved to delay disease progression in FC II and III patients[1]

Kaplan-Meier estimates of risk of first primary endpoint event in SERAPHIN



Disease progression included: death, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms and need for additional PAH treatment).[1]

***Patients on PAH-specific background therapy at baseline**



Summary of primary endpoint events

	OPSUMIT 10 mg (n=242) n (%)	Placebo (n=250) n (%)
Patients with a primary endpoint event†	76 (31.4)	116 (46.4)
Component as first event		
Worsening PAH	59 (24.4)	93 (37.2)
Death	16 (6.6)	17 (6.8)
IV/SC prostanoid	1 (0.4)	6 (2.4)

The beneficial effect of OPSUMIT was primarily attributable to a reduction in clinical worsening events (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).[1]

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

WARNINGS AND PRECAUTIONS (continued)

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

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

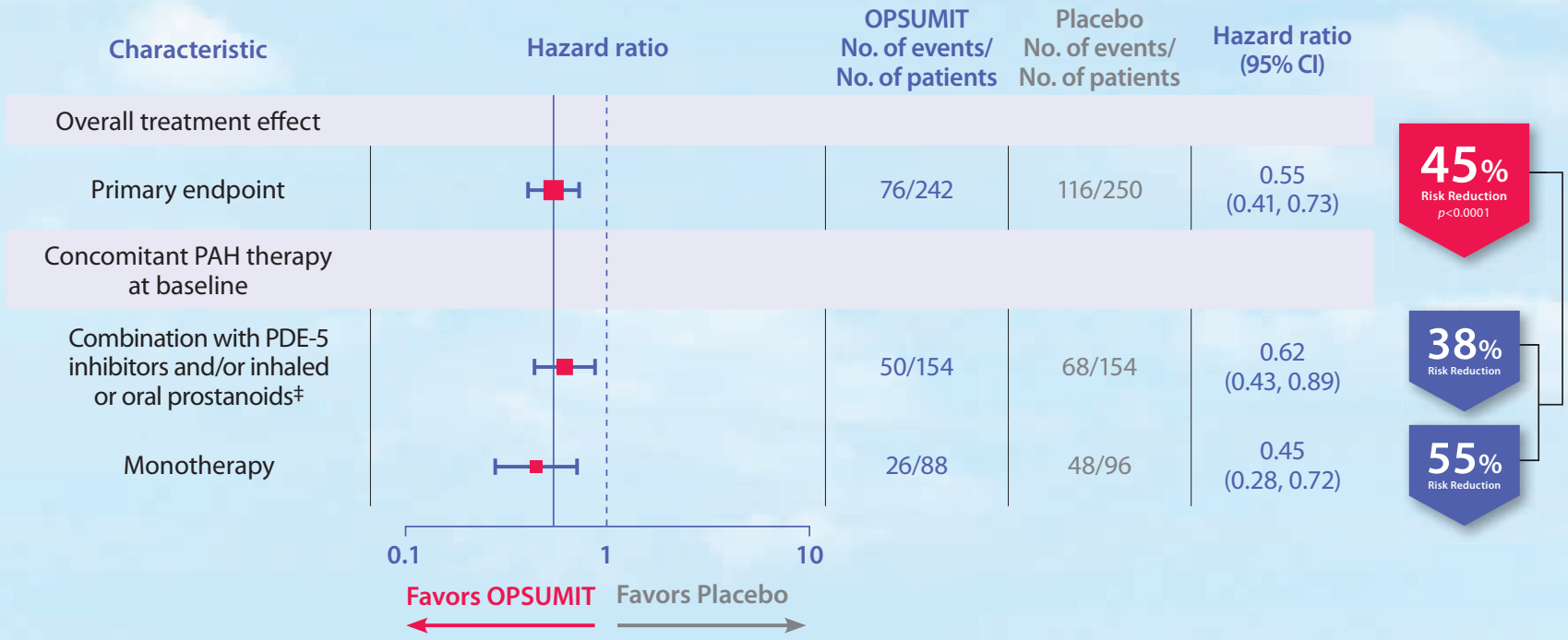
Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

INDICATION (continued)

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 were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. 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%).

OPSUMIT provided consistent efficacy on the primary endpoint as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

Subgroup analysis of the primary endpoint in the SERAPHIN study



‡The OPSUMIT indication includes combination with phosphodiesterase-5 inhibitors or inhaled prostanoids, but not oral prostanoids.

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

Don't delay, treat today—keep disease progression in mind from the start of therapy in FC II and III patients.

OPSUMIT is approved for use as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

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.

References: 1. OPSUMIT full prescribing information. Actelion Pharmaceuticals US, Inc. February 2015. **2.** Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809-818. **3.** Center for Drug Evaluation and Research, Food and Drug Administration. Opsumit (macitentan) NDA 204410. Medical Review(s). 19 October 2013. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000MedR.pdf. Accessed April 15, 2015.

CI: confidence interval; CYP: cytochrome P450; FC: functional class; HIV: human immunodeficiency virus.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

ACTELION

FUTURE. FORWARD. Opsumit® macitentan tablets 10 mg

Opsumit®
macitentan tablets 10 mg

Rx only

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 (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), Use in Specific Populations (Pregnancy)]*.**
- **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 Use in Special Populations (Females and Males of Reproductive Potential)]*.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (OPSUMIT REMS Program)]*.**

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 delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced 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 were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. 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%).

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, apprise the patient of the potential hazard to a fetus [see *Warnings and Precautions (Embryo-fetal Toxicity)* and *Use in Specific Populations (Pregnancy)*].

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 section 2.2 in full Prescribing Information* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

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

OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT 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 (Females and Males of Reproductive Potential)*].
- 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.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other 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.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 × ULN	3.4%	4.5%
>8 × 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.

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 × 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.

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 (Clinical Trial Experience)*].

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

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see *Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)*].

ADVERSE REACTIONS

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

- Embryo-fetal Toxicity [see *Warnings and Precautions (Embryo-fetal Toxicity)*]
- Hepatotoxicity [see *Warnings and Precautions (Hepatotoxicity)*]
- Decrease in Hemoglobin [see *Warnings and Precautions (Hemoglobin Decrease)*]

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). 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%).

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)
Respiratory, thoracic and mediastinal disorders: nasal congestion

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 (Pharmacokinetics)*].

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 (Pharmacokinetics)*]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see *Clinical Pharmacology (Pharmacokinetics)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications (Pregnancy)*].

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.

Nursing Mothers

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

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.

Females and Males of Reproductive Potential

Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see *Boxed Warning* and *Dosage and Administration section 2.2 in full Prescribing Information*].

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 *Boxed Warning*].

Males

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see *Warnings and Precautions (Decreased Sperm Counts)* and *Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility*].

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.

OPSUMIT® (macitentan)

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

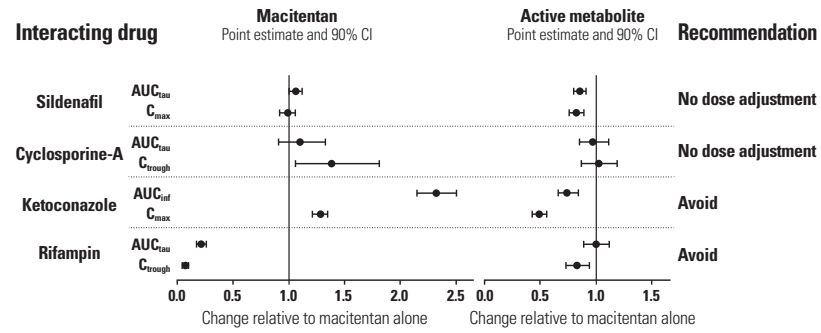
In vitro studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

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 (Strong CYP3A4 Inhibitors)*].

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.

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.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20150219

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Anticoagulant effect reversed

Idarucizumab *from page 1*

with NOAC use, and patients taking one of these agents occasionally require urgent surgery or other intervention for which normal hemostasis is required," added Dr. Pollack, chair of the emergency medicine at Pennsylvania Hospital in Philadelphia.

In RE-VERSE AD (a study of the reversal effects of idarucizumab on active dabigatran), the first 90 patients were divided into two distinct groups. Group A, with 51 patients, included those on dabigatran with serious bleeding. Group B, with 39 patients, required reversal of dabigatran for urgent or emergent procedures.

In both groups, idarucizumab provided a median maximum reversal of 100% (95% confidence interval, 100-100) of the anticoagulation effect within 4 hours.

Clotting assays were normalized almost immediately in almost 90% of patients, and the effect was durable, with 80% having measured dabigatran levels reflecting no significant anticoagulation 24 hours later.

"Clinical outcomes were quite good in this multimorbid patient population, with restoration of hemostasis as reported by local investigators achieved in less than 12 hours when assessable, and with 92% of surgical patients being reported as having normal hemostasis at the time of the procedure," Dr. Pollack said.

"There were no serious adverse events related to the reversal agent ... one patient experienced a thrombotic complication within 72 hours, and that patient had not been restarted on any antithrombotics," he said.

"The study is ongoing," he added, "but these interim results show rather convincingly that idarucizumab completely and safely reverses the anticoagulant effects of dabigatran within minutes."

In addition, Dr. Pollack said the availability of a specific reversal agent for dabigatran would enhance its safety margin, and thus alleviate the fears of providers who may hesitate to use a NOAC because of the lack of an "antidote."

"In fact, most such cases can already be successfully and safely managed with general support and 'tincture of time' (the half-life of dabigatran is much shorter than that of warfarin), but having a specific 'go-to' option could streamline the care of the most significantly compromised patients," he said.

Dr. Pollack emphasized, however, that idarucizumab is a specific reversal agent for dabigatran, not an antidote. "To me, the latter would imply that idarucizumab immediately stops bleeding associated with active use of dabigatran," he said.

Providers should realize that while idarucizumab seems capable of removing dabigatran-induced coagulopathy from the list of concerns when managing a patient with serious bleeding or before a "sharp" procedure, bleeding is a multifaceted issue that also may be due to traumatized blood vessels, other causes of coagulopathy such as liver disease, or concurrent use of antiplatelet medications, he said.

"The patient with a serious or life-threatening bleed on dabigatran will likely need additional care to investigate and manage such concerns," Dr. Pollack said. "But at least idarucizumab can specifically, safely, and rapidly address the primary consideration.

"The safety of anticoagulation therapy with dabigatran is further enhanced with idarucizumab, a specific reversal agent that won't need to be used often, but the availability of which would be reassuring to prescribers," he concluded.

Boehringer Ingelheim sponsored RE-VERSE AD.

Idarucizumab was given a fast-track status by the Food and Drug Administration, and BI submitted a new drug application in March 2015, the company reported.

VITALS

Key clinical point: The investigational monoclonal antibody idarucizumab reversed the anticoagulant effects of dabigatran.

Major finding: Idarucizumab provided a median maximum dabigatran reversal of 100% (95% CI, 100-100) of the anticoagulation effect within 4 hours in an interim analysis.

Data source: RE-VERSE AD, a prospective cohort study in which 90 patients treated with dabigatran who had uncontrolled bleeding or required emergency surgery or procedures were given 5.0 g idarucizumab.

Disclosures: Boehringer Ingelheim sponsored RE-VERSE AD. Dr. Pollack reported receiving personal fees from Boehringer Ingelheim, Janssen, Daiichi-Sankyo, Bristol-Myers Squibb, and Pfizer. Disclosures for all the investigators are available at NEJM.org.

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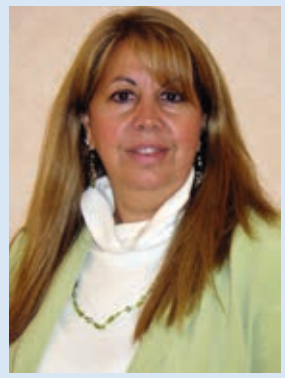

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COPD-like Symptoms

Gold 0 *from page 1*

ping exceeding 20%, (seen in 12.2%), St. George's Respiratory Questionnaire (SGRQ) total score exceeding 25 (seen in 26%), and a 6-minute walk distance of less than 350 m (seen in 15.4%).

In 108 never smokers, none had chronic bronchitis or respiratory exacerbations, 3.7% had dyspnea, 8.3% had quantitative emphysema exceeding 5%, 10.2% had quantitative gas trapping exceeding 20%, 3.7% had SGRQ scores above 25, and 3.7% had a 6-minute walk distance of less than 350 m.

Dr. Regan, of National Jewish Health and the University of Colorado, Denver, and her associates gathered data from 21 sites across the United States regarding 8,872 current or former smokers who were between the ages of 45 and 80 years.

The subjects were classified using GOLD spirometric criteria based on postbronchodilator spirometry: 4,388 had a GOLD 0 score, defined as a normal postbronchodilator ratio of FEV_1 to forced vital capacity exceeding 0.7 and an FEV_1 percentage of at least 80% predicted; 794 patients had a GOLD 1 score, defined as mild COPD; and 3,690 had a GOLD 2-4 score, defined as moderate to severe COPD.

Compared with 108 never smokers, the GOLD 0 group had a worse quality of life score (mean SGRQ total score 17.6 for GOLD 0 and 7 for never smokers) and a lower 6-minute walk distance (447 m for GOLD 0 vs. 493 m for never smokers).

In a subset of 300 patients in the GOLD 0 group whose CT scans were visually scored, 42% (127) had evidence of emphysema or airway thickening.

In a subset of 100 never smokers, 10% had evidence of emphysema or airway thickening.

Current guidelines do not include recommendations on treating smokers with normal spirometry results, but physicians recognize the role of medication in treating symptoms and effective treatments need to be determined for GOLD 0 patients, the researchers said.

Respiratory medications were being prescribed to 20% of the GOLD 0 participants in COPDGene who had at least one impairment, yet these patients reported more symptoms.

VITALS

Key clinical point: Up to 35 million current and former smokers older than age 55 years may have COPD-like respiratory-related impairment.

Major finding: Of 4,388 current and former smokers older than age 55 years who did not meet the spirometric criteria for COPD (GOLD 0 score), 55% had significant respiratory disease.

Data source: The COPDGene study, one of the largest studies ever to investigate the underlying genetic factors of COPD, plans to enroll 10,000 individuals.

Disclosures: The COPDGene study is sponsored by funding from the National Heart, Lung, and Blood Institute and the COPD Foundation through contributions made to an industry advisory board representing AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovian, and GlaxoSmithKline.

OSA gets missed in CVD patients

Sleep and Stent Study *from page 1*

conference of the American Thoracic Society.

Of 1,305 patients included in the ongoing observational study, 45% had OSA, including 21.8% who had severe OSA defined by an apnea-hypopnea index of 30 or more events/hour, she said..

Excessive daytime sleepiness, defined as an Epworth Sleepiness Scale score of greater than 10, was identified in 24.5% of the OSA patients, and a Berlin Questionnaire score indicative of high risk for OSA was found in 54.3% of patients with OSA, said Dr. Furlan, who is with the University of Sao Paulo, Brazil.

The adverse event rate was 11%

Tools for OSA risk in the general population may not be useful in those with cardiovascular disease.

DR. FURLAN

VITALS

Key clinical point: OSA presents differently in CAD patients, so traditional diagnostic criteria will miss a large proportion of cases.

Major finding: 24.5% of the OSA patients reported excessive daytime sleepiness, and only 54.3% had a Berlin Questionnaire score indicative of high risk for OSA.

Data source: A multicenter observational study involving 1,305 patients.

Disclosures: The investigators reported having no disclosures. The Sleep and Stent Study is sponsored by Boston Scientific Corporation.

in CAD patients with OSA, compared with 6.5% in those without OSA – a significant difference thus far in the study, Dr. Furlan noted.

Patients in the Sleep and Stent Study, which was designed to look at relationships between OSA and cardiovascular outcomes among adults treated with percutaneous coronary intervention, were aged 18-80 years and were enrolled from eight centers in five countries: Singapore, China and Hong Kong, India, Myanmar, and Brazil.

Continued on following page

Continued from previous page

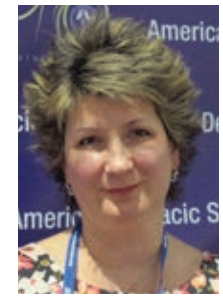
Indications for percutaneous coronary intervention included ST segment elevation myocardial infarction in 33% of subjects, non-ST segment elevation myocardial infarction in 20% of subjects, unstable angina in 16% of subjects, and stable angina in 31% of subjects.

All patients underwent an overnight sleep study using a level-3 portable diagnostic device prior to hospital discharge, and the tracings were analyzed by a blinded sleep physician.

The prevalence of OSA was comparable across study sites, Dr. Furlan said.

The findings reinforce the known association between OSA and cardiovascular disease, lead researcher Dr. Luciano Drager, also of the University of Sao Paulo, said in a press statement.

"Earlier studies have shown strong relationships between sleep



Patients with heart attacks and severe coronary artery disease did not report being sleepy.

DR. TEODORESCU

apnea and a number of cardiovascular conditions, including high blood pressure, arrhythmia, stroke, and heart failure.

"Our study supports this strong association between OSA and heart disease and also suggests that the methods used to screen for OSA in patients with cardiovascular disease need to be improved," Dr. Drager said.

Given the apparent association that exists between sleep apnea and adverse outcomes in patients with cardiovascular disease, and the fact that sleep apnea is underdiagnosed, it may be time to consider monitoring for sleep apnea in cardiovascular disease patients, Dr. Furlan added.

Non–sleep related predictors of OSA in patients with cardiovascular disease also should be explored, she said.

Press briefing moderator Dr. Mihaela Teodorescu of the University of Wisconsin, Madison, observed that other studies also have suggested that coexistent OSA manifests differently in different disease states.

"This is a very good example. Whereas in the general population sleepiness is one of the major presenting symptoms, in this particularly vulnerable population with heart attacks and severe coronary artery disease, these people are not sleepy, " she said, adding that "current screening questionnaires, which are relatively widely used in clinical populations, may not do the job."

In fact, if traditional criteria for diagnosis are used, a large proportion of patients with OSA will be missed, she said.

"To me as a clinician, this is the major take-home message: Don't rely on symptoms, because we will miss a large proportion of patients simply based on that."

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VIEW ON THE NEWS

David A. Schulman, MD, FCCP comments: While a growing amount of evidence supports the association between obstructive sleep apnea and cardiovascular disease, the study presented by Dr. Furlan raises some fascinating questions about how aggressively we should screen for OSA in the post-percutaneous coronary intervention population.

It isn't surprising that the prevalence of sleep-disordered breathing in this population is almost 50%, but it is troubling that so many failed to report the classic sleepiness associated with OSA. Whether this is due to an actual difference in the manifestation of the disease or a masking of symptoms due to patient attribution of their fatigue to known cardiovascular pathology is unclear; in either circumstance, it suggests that currently-available screening tools may be much less useful in patients with prevalent coronary disease, who may benefit from polysomnography or portable sleep monitoring to mitigate the risk of future cardiovascular events.

Sleep Strategies: Burning the midnight oil

BY SHERYLL SORIANO, MD, AND ANEESA DAS, MD, FCCP

Since the use of oil burning lamps, followed by the invention of the light bulb by Thomas Edison, there has been a steady growth of nocturnal work. With the increasing demand worldwide to sustain our 24-hour society, it has been estimated that nearly 20% of the labor force worldwide involves work shifts outside the traditional 8:00 AM to 5:00 PM workday (Valentina et al. *Sleep*. 2014;37[3]:545). Leading this trend is the United States (as seen in the Figure). Shift work is even common in occupations that directly affect the health and safety of others, such as transportation and health care.

DR. DAS

DR. SORIANO

Shift work can cause a disruption of our circadian sleep-wake pattern and can often lead to sleep deprivation. Shift work disorder (SWD) is established when this misalignment between the timing of the sleep/wake cycle causes sleep disturbance, insomnia, sleepiness, fatigue, and impaired daytime function. The 2008 Sleep in America Poll assessed sleep and the workplace. The poll found that 58% of shift workers (defined as workers who start their job after 6:00 PM but before 6:00 AM) reported less than 6 hours in bed on workdays compared with 13% of nonshift workers. Shift workers worked more hours per week, were more likely to have other sleep disorders, and were more likely to drive drowsy. Recently reported cross-sectional data from the population-based Survey of the Health of Wisconsin (SHOW), collected from 2008 to 2012, showed that shift workers are more commonly men, minorities, and with lower levels of education (Givens et al. *Sleep Health*. 2015;1:115).

Shift work is more prevalent in blue-collar workers. However, white-collar nocturnal work is increasing as well. According to the US Bureau of Labor Statistics, between 1991 and 1997, there was an 11% increase in the number of white-collar employees working nights compared with only a 6% increase among blue-collar employees (Mcmenamin, *Monthly Labor Review*. 2007;Dec:3).

A potential health risk

Shift workers and those with SWD may be at greater risk for many health concerns. The SHOW data found shift workers to be more overweight than traditional schedule workers and reported more sleep problems, such as insomnia symptoms, insufficient sleep, and sleepiness. Shift workers have an increased risk of sleep disorders, cardiovascular disorders, obesity, and cancer.

Regarding cardiovascular disorders, shift work has been associated with coronary artery disease, hypertension, and cardiovascular death. The risk of death from heart disease was 19% higher among those who worked rotating night shifts for 6 to 14 years and 23% higher for those who worked rotating night shifts for 15 or more years according to the Nurses' Health Study (Gu et al. *Am J Prev Med*. 2015;48[3]:241). While numerous studies have suggested higher prevalence of cardiovascular disease among shift workers, a clear causal pathway has not been established.

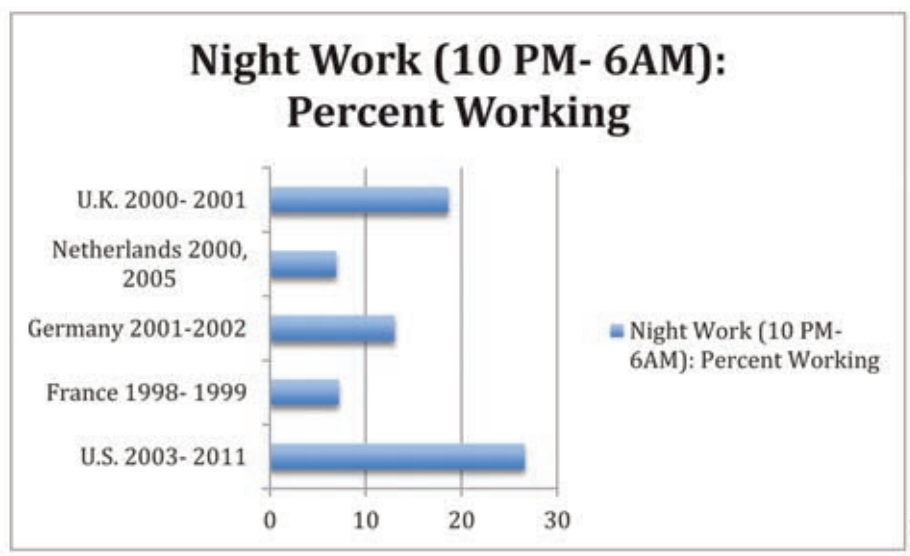
Possible explanations for the increased cardiovascular disease include circadian stress along with behavioral changes, such as decreased physical activity and dietary changes in night shift workers. Shift work and sleep deprivation can lead to insulin resistance and type 2 diabetes, which can further increase cardiovascular risk. Other theories suggest physiologic stress, such as autonomic dysfunction, cortisol dysregulation affecting inflammation, or endothelial dysfunction.

Shift work has recently been associated with malignancy. Most notably, shift work has been associated with breast cancer. This risk appears to be greatest with prolonged rotating night shift early in one's career (Schernhammer. *Occup Environ Med*. 2014;71[1 Suppl]:A121). The relationship between shift work and breast cancer is likely related to the changes in the circadian melatonin levels due to nocturnal exposure to light through multiple pathways (Hill et al. *Endocr Relat Cancer*. 2015;22[3]:R183). Recent data from the Nurses' Health Study report a 25% increased risk of lung cancer among women working rotating shifts for more than 15 years compared with those working no night shifts. There is limited and inconsistent evidence for an association between shift work and prostate and colon cancers.

Irregular work hours not only result in physiologic stress but also psychosocial stress. With greater difficulties controlling personal hours, decrease work-life balance, and insufficient recovery sleep, family and social relationships are vulnerable to deterioration. This chronic "social jet lag" is associated with sleep deprivation, absenteeism, and depression.

Working during our circadian-predicted sleep phase can be associated with sleepiness at work. Risk for errors and accidents appear to be higher in shift workers with nearly three-fold increased risk of occupational and commute-to-home accidents compared with day workers (Swanson et al. J Sleep Res. 2011;20[3]:487). There is reported increased risk of motor vehicle accidents in health-care workers and police and commercial drivers working nights compared with those who do not work night shifts (Wright et al. *Sleep Med Rev*. 2013;17[1]:41). Risk of vehicular, aviation, and industrial accidents are highest at night, especially in the early morning hours.

Shift workers worked more hours per week, were more likely to have other sleep disorders, and were more likely to drive drowsy



Work hours in the United States and elsewhere.
(adapted from Hamermesh et al. 2014. Long work weeks and strange hours. National Bureau of Economic Research.)

ACCP

What can we do?

As health-care providers treating sleep disorders, we commonly encounter shift workers and SWD. It is our responsibility to identify these at-risk patients and provide early intervention. Optimally, shift workers should attempt to sleep immediately after their night shift. Promoting good sleep hygiene is essential; restricting caffeine and alcohol consumption prior to bedtime, and turning off phones and other electronic devices during daytime sleep prevents disturbance. It is also important to educate family members regarding the need for protected sleep time for shift workers.

Administration of melatonin prior to daytime sleep may help to phase-shift the sleep period and provide a soporific effect. However, the data have not definitively supported improvements in sleep with morning (AM) melatonin use. Appropriately timed light exposure is critical to adaptation to a nocturnal schedule. Use of bright light during the first half of the night shift and increasing outside light exposure in the evening prior to starting one's shift can phase delay the circadian pacemaker. Likewise, avoiding bright light on the ride home and in the morning is necessary to fully adapt to a night schedule. This can be done with use of dark sunglasses on the ride home. The scheduled daytime sleep period should be done in a dark room.

Ideally, those working night shifts should maintain their nocturnal schedule even on days off to allow them to stay in circadian phase. However, this is often not practical with family and personal responsibilities. Adjuncts to optimize workplace alertness and safety may be used.

Continued on following page

LAW & MEDICINE: Auto accidents in sleepy medical trainees

BY S.Y. TAN, M.D., J.D.
Frontline Medical News

Question: Driving home after a demanding 24 hours on call, the sleepy and fatigued first-year medical resident momentarily dozed off at the wheel, ran a stop sign, and struck an oncoming car, injuring its driver. In a lawsuit by the injured victim, which of the following answers is best?


DR. TAN

A. The residency program is definitely liable, being in violation of Accreditation Council for Graduate Medical Education rules on consecutive work hours.

B. The resident is solely liable, because he's the one who owed the duty of due care.

C. The hospital may be a named codefendant, because it knew or should have known that sleep deprivation can impair a person's driving ability.

D. A and C are correct.

E. Only B and C are correct.

Answer: E. Residency training programs face many potential liabilities, such as those arising from disciplinary actions, employer-employee disputes, sexual harassment, and so on. But one issue deserving attention is auto accidents in overfatigued trainees. The incidence of falling asleep at the wheel is very high – in some surveys, close to 50% – and accidents are more likely to occur in the immediate post-call period.

The two main research papers documenting a relationship between extended work duty and auto accidents are from Laura K. Barger, Ph.D., and Dr. Colin P. West.

In the Barger study, the authors conducted a nationwide Web-based survey of 2,737 interns (N. Engl. J. Med. 2005;352:125-34). They found that an extended work shift (greater than 24 hours) was 2.3 times as likely for a motor vehicle crash, and 5.9 times for a near-miss accident. The researchers calculated that every extended shift in the month increased the crash risk by 9.1% and near-miss risk by 16.2%.

In the West study, the authors performed a prospective, 5-year longitudinal study of a cohort of 340 first-year Mayo Clinic residents in internal medicine (Mayo Clin. Proc. 2012;87:1138-44). In self-generated quarterly filings, 11.3% reported a motor vehicle crash and 43.3% a near-miss accident. Sleepiness (as well as other variables such as depression, burnout, diminished quality of life, and fatigue) significantly increased the odds of a motor vehicle incident in the subsequent 3-month period. Each 1-point increase in fatigue or Epworth Sleepiness Scale score was associated with a 52% and 12% respective increase in a motor vehicle crash.

The Accreditation Council for Graduate Medical Education (ACGME) has formulated rules, which have undergone recent changes, regarding consecutive work-duty hours. Its latest edict in June 2014 can be found on its website and stipulates that "Duty periods of PGY-1 residents must not exceed 16 hours in duration," and "Duty periods of PGY-2 residents and above may be scheduled to a maximum of 24 hours of continuous duty in the hospital."

Furthermore, programs must encourage residents to use alertness management strategies in the context of patient care responsibilities. Strategic napping, especially after 16 hours of continuous duty and between the hours of 10:00 p.m. and 8:00 a.m., was a strong suggestion.

In a 2005 lawsuit naming Chicago's Rush Presbyterian-St. Luke's Medical Center as a defendant, an Illinois court faced the issue of whether a hospital owed a duty to a plaintiff injured by an off-duty resident doctor allegedly suffering from sleep deprivation as a result of a hospital's policy on working hours (*Brewster v. Rush Presbyterian-St. Luke's Medical Center* (836 N.E.2d 635 (Il. App. 2005)). The doctor was an intern who had worked 34 hours of a 36-hour work shift, and fell asleep behind the wheel of her car, striking and seriously injuring the driver of an oncoming car.

In its decision, the court noted the plaintiff's argument that it was reasonably foreseeable and likely that drivers who were sleep deprived would cause traffic accidents resulting in injuries. For public policy reasons, the plaintiff also maintained that such injuries could be prevented if hospitals either changed work schedules of their residents or provided them with additional rest periods.

However, the court held that there was no liability imputed to health care providers for injuries to nonpatient third parties absent the existence of a "special relationship" between the parties.

Thus, training programs or hospitals may or may not be found liable in future such cases or in other jurisdictions – but the new, stricter ACGME rules suggest that they will, at a minimum, be a named defendant.

Note that in some jurisdictions, injured nonpatient third parties have successfully sued doctors for failing to warn their patients that certain medications can adversely affect their driving ability, and for failing to warn about medical conditions, e.g., syncope, that can adversely impact driving.

Court decisions in analogous factual circumstances have sometimes favored the accident victim.

In *Robertson v. LeMaster* (301 S.E.2d 563 (W. Va. 1983)), the West Virginia Supreme Court of Appeals noted that the defendant's employer, Norfolk & Western Railway Company, "could have reasonably foreseen that its exhausted employee, who had been required to work 27 hours without rest, would pose a risk of harm to other motorists."

In *Faverty v. McDonald's Restaurants of Oregon* (892 P.2d 703 (Ore. Ct. App.1995)), an Oregon appeals court held that the defendant corporation (McDonald's Restaurants of Oregon) knew or should have known that its employee was a hazard to himself and others when he drove home from the workplace after working multiple shifts in a 24-hour period.

An extended work shift (greater than 24 hours) was 2.3 times as likely for a motor vehicle crash, and 5.9 times for a near-miss accident.

On the other hand, in *Barclay v. Briscoe* (47 A.3d 560 (Md. 2012)), a longshoreman employed by Ports America Baltimore fell asleep at the wheel while traveling home after working a 22-hour shift and caused a head-on collision resulting in catastrophic injuries. Ports America Baltimore contended that it could not be held primarily liable, because it owed no duty to the public to ensure that an employee was fit to drive his personal vehicle home. The trial court agreed, and the Maryland Court of Appeals affirmed.

Dr. Tan is emeritus professor of medicine and former adjunct professor of law at the University of Hawaii, and currently directs the St. Francis International Center for Healthcare Ethics in Honolulu. This article is meant to be educational and does not constitute medical, ethical, or legal advice. Some of the articles in this series are adapted from the author's 2006 book, "Medical Malpractice: Understanding the Law, Managing the Risk," and his 2012 Halsbury treatise, "Medical Negligence and Professional Misconduct." For additional information, readers may contact the author at siang@hawaii.edu.

Sleep Strategies *Continued from previous page*

Caffeine use may enhance alertness during the night shift. Napping in the afternoon before starting a night shift and for brief periods throughout the night can be effective in improving alertness. More workplaces are providing sleep rooms to facilitate naps during work hours.

A final option to promote sleep and optimize alertness is with the aid of pharmaceuticals. Hypnotic medications may be used to promote daytime sleep among night shift workers with persistent difficulty initiating sleep and adjusting their circadian phase. However, carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. The nonamphetamine wakefulness promoting medications, including modafinil and armodafinil, can enhance alertness during the night shift for SWD. Their use in SWD is studied in clinical trials and is currently approved by the FDA for this indication.

Shift work is unavoidable in our present 24-hour society; therefore, a substantial proportion of the population is at risk for SWD. Cessation of shift work is curative but may not be an option. All shift workers will likely benefit from education about ways to promote circadian adaptation, increase wakefulness, improve sleep hygiene, increase sleep duration, and promote good health practices. Clinical practice guidelines for shift work and SWD are founded on evidence-based medicine.

Dr. Soriano and Dr. Das are with the Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine; The Ohio State University; Columbus, Ohio.

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Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

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

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

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

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Esbriet®
(pirfenidone) capsules 267 mg

Proven to delay progression in IPF[1]

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had ≥10% decline in %FVC, $P<0.001$). Treatment effect was evident at 13 weeks ($P<0.001$) and increased through trial duration[1,2,*,†]
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)[2,*,‡]
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet[2]
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide[3]

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

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

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

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the ≥10% decline category.
‡Stable was defined as no decline in lung function.

References: 1. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. **2.** Esbriet full Prescribing Information. InterMune, Inc. October 2014. **3.** InterMune, Inc. Data on file.

Genentech
A Member of the Roche Group

Esbriet®
(pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

ADVERSE REACTIONS

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

- Liver Enzyme Elevations *[see Warnings and Precautions]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions]*
- Gastrointestinal Disorders *[see Warnings and Precautions]*

Clinical Trials Experience

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

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

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

Table 1. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

DRUG INTERACTIONS

CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration section 2.4 in full Prescribing Information]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

ESBRIET® (pirfenidone)

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.2 in full Prescribing Information]*.

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information],* which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005 USA

INTERMUNE®

FDA panel gives nod to mepolizumab for adults

BY KARI OAKES
Frontline Medical News

GAITHERSBURG, MD.– Mepolizumab was unanimously recommended for approval as a treatment for severe asthma in adults at a meeting of the Food and Drug Administration's Pulmonary-Allergy Drugs Advisory Committee.

All 14 members of the advisory panel agreed that the efficacy data provide substantial evidence of a clinically meaningful benefit of mepolizumab for the treatment of severe asthma in adults; 13 of the 14 members agreed that the data adequately demonstrated safety in adults.

However, only four panel members recommended approval for adolescents aged 12-17 years, with the majority of panel members citing concerns that the low number of adolescents studied to date did not allow safety to be adequately evaluated in a younger population, especially for a medication that would be taken for many years – perhaps for a lifetime.

If approved by the FDA, the biologic agent would be available as a once-monthly treatment that is injected subcutaneously by a health care professional. Mepolizumab would be marketed by Glaxo Smith Kline under the trade name Nucala.

Mepolizumab is a first-in-class humanized monoclonal antibody that targets interleukin-5, a glycoprotein cytokine that mediates production of eosinophils. Elevation of eosinophils in blood and tissue is associated with an increase in cytokines and other inflammatory molecules that can trigger or exacerbate airway inflammation in asthma. One other monoclonal antibody, the anti-IgE biologic omulizimab (Xolair), has been approved to treat asthma.

FDA NEWS

Glaxo Smith Kline brought mepolizumab to the FDA for use as an add-on therapy for the small subset of asthma patients whose disease remains uncontrolled despite the optimal use of inhaled corticosteroids and additional therapies such as leukotriene inhibitors or theophylline. This population experiences more frequent asthma exacerbations, has more emergency department visits and hospitalizations, and uses higher doses of oral corticosteroids. Approximately 60% of those with severe asthma have marked eosinophilia.

Panel members uniformly cited the efficacy data for adults with severe asthma; several panelists also remarked on the importance of developing more steroid-sparing alternatives for this population.

The panel endorsed neither efficacy nor safety for those aged 12-17 years, with 9 of the 14 panelists voting not to endorse efficacy and 13 members voting not to endorse safety findings. Mepolizumab's efficacy, many panelists said, was not clearly established from the data presented, which drew from small numbers of adolescents enrolled in the studies.

Dr. David Au, acting director of Health Services Research and Development at Seattle's VA Puget Sound Health Care system, observed that "adolescents are not small adults – their lungs continue to mature over time." Many panelists, however, also called for ongoing study, noting the significant unmet need for steroid alternatives in the adolescent population.

Several panelists advocated postmarketing surveillance for long-term use, with particular attention to those with parasitic disease, to monitoring any sign of malignancy, and to tracking opportunistic diseases such as herpes zoster.

An early clinical trial of mepolizumab, conducted in 1999, failed to show benefit for an undifferentiated population of patients with moderate to severe asthma. However, independent research later identified marked eosinophilia as a factor associated with more frequent asthma exacerbations and a series of clinical trials begun in 2011 targeted patients with severe asthma and eosinophilic inflammation. A global program was initiated, with 12% of patients overall coming from the United States.

Pivotal phase 2b/3, double blind, placebo-controlled clinical trials included a dose-ranging study tracking asthma exacerbations enrolling 616 patients for 52 weeks.

The recommended dose of 100 mg subcutaneously every 4 weeks, as well as a 75-mg IV dose, was used for an additional 576 patients for 32 weeks, with the primary outcome measure being the number of asthma exacerbations. A final 24-week study of 135 patients with severe asthma measured the reduction in oral corticosteroid use, compared with placebo, as well as the number of asthma exacerbations. In all of the studies, patients' asthma treatment was optimized according to standard of care before adding mepolizumab.

In each study and in pooled data, mepolizumab approximately halved the number of asthma exacerbations for study participants when compared with those using placebo. A 24-week corticosteroid-sparing study showed significant reduction in oral corticosteroid use, without loss of asthma control, for the mepolizumab group. Prespecified subgroup analyses were hampered because of low participation numbers for African Americans and adolescents, and because confidence intervals for these subgroups often ranged over 1, limiting interpretation of benefit results for these groups.

The overall safety profile was good, with adverse event rates similar in the treatment and placebo arms. Headache and injection-site reactions were the most commonly reported adverse events but were similar between treatment and placebo arms. No episodes of anaphylaxis were reported, and neutralizing antibodies developed in one patient total across all studies. Ongoing open-label studies continue.

The FDA's independent biostatistical analysis showed clear evidence of efficacy for mepolizumab, with demonstrated consistent, statistically significant decreases of about one exacerbation per year, according to the agency.

The agency observed a positive association between higher eosinophil count and mepolizumab treatment effect, meaning that those with higher eosinophil counts saw a greater benefit from mepolizumab, as measured by a reduction in exacerbations.

The number of deaths was balanced across treatment arms, though a larger number of respiratory-related deaths than expected was seen overall. This higher number of deaths may reflect the severity of asthma in the study population. The respiratory-related serious adverse events, according to the FDA, favor treatment over placebo.

No treatment-related cardiovascular risks were identified.

The FDA usually follows the recommendations of its advisory panels. The FDA panelists reported no relevant conflicts of interest.

Mepolizumab more effective in elderly asthma patients

BY SHARON WORCESTER
Frontline Medical News

DENVER – The rate of asthma exacerbations was reduced more among elderly patients than among younger patients treated with mepolizumab vs. placebo as part of the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) trial, according to a post hoc analysis of the trial data.

Mepolizumab improved quality of life, compared with standard care, in both older and younger patients, although little differentiation was seen with respect to asthma control, Dr. Hector Ortega reported in a poster at an international conference of the American Thoracic Society.

A 76% greater reduction in clinically significant exacerbations was seen in 54 mepolizumab-treated patients aged 65 years and older in the trial, compared with 26 in that age group who received placebo (mean exacerbation rate per year, 0.92 vs. 1.65); a 44% greater reduction was seen in 331 mepolizumab-treated patients under age 65 years, compared with 165 in that age group who received placebo (mean exacerbation rate per year, 0.42 vs. 1.78), said Dr. Ortega, medical director at GlaxoSmithKline, Research Triangle Park, N.C.

The adjusted mean difference vs. placebo in change in St. George's Respiratory Questionnaire scores from baseline to 32 weeks was -4.5 in the

Continued on following page

VITALS

Key clinical point: The rate of asthma exacerbations was reduced more among elderly patients than among younger patients treated with mepolizumab vs. placebo.

Major finding: The mean reduction in the exacerbation rate with mepolizumab vs. placebo was 76% for those aged 65 and older vs. 44% in those under age 65.

Data source: A post hoc analysis of data from 576 patients in the multicenter, randomized, placebo-controlled MENSA trial.

Disclosures: The trial and post hoc analysis were funded by GSK. Dr. Ortega is employed by GSK.

Are steroid/LABA regimens overused in mild COPD?

BY SHARON WORCESTER
Frontline Medical News

DENVER – Inhaled corticosteroid plus long-acting beta$_2$-agonist therapy is overused in patients with mild COPD, based on a post hoc analysis of two pivotal phase III studies.

At entry in the TONADO studies, nearly 40% of patients who were classified as having GOLD A or B disease were receiving ICS maintenance therapy either alone, in free combination, or as fixed-dose combination therapy, Dr. Henrik Watz of the Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Center North, Grosshansdorf, Germany, and his colleagues reported at an international conference of the American Thoracic Society.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that use of inhaled corticosteroids (ICS) and long-acting beta$_2$-agonist (LABA) therapy be restricted to patients with severe or very severe COPD (category C or D disease) with frequent exacerbations.

The post-hoc analysis "confirms previous reports highlighting that treatment regimens containing ICS therapy are being used early in the management of patients with COPD, which may not be appropriate based on current GOLD recommendations. Furthermore, consistent improvements in lung function with tiotropium plus olodaterol versus the monocomponents were demonstrated in GOLD A, B, C, and D, regardless of previous ICS use," Dr. Watz and his associates concluded.

The replicate TONADO studies (TONADO 1 and 2) were multicenter, randomized, double-blind, active-controlled studies evaluating the once-daily long-acting muscarinic agent (LAMA) tiotropium and the LABA olodaterol. The 5,162 patients were randomized to once-daily treatment with inhaled tiotropium plus olodaterol (Respimat FDC), to tiotropium, or to olodaterol for 52 weeks.

Of the study participants, 2,132 had GOLD A/B disease, and 3,030 had GOLD C/D disease, based on exacerbation history and lung function. All had postbronchodilator forced expiratory volume in 1 second (FEV_1) that was less than 80% of predicted normal, and FEV_1/forced vital capacity of less than 70%. All were current or exsmokers with a history of more than 10 pack-years.

At study entry, 7.2% of the GOLD A/B patients were treated with ICS without a LABA, and 31.1% were receiving ICS and a LABA. Of the GOLD C/D patients, 8.8% were receiving ICS without a LABA and 45% were receiving ICS with a LABA.

During the study, those who received both tiotropium and olodaterol had significant improvements in lung function, compared with those receiving only tiotropium. Among patients who had previously used ICS and received both drugs, the FEV_1 area under the curve at 0-3 hours was 0.310 L for GOLD A/B patients and 0.236 L for GOLD C/D patients. For those with no prior ICS use, the FEV_1 area under the curve at 0-3 hours was 0.277 L for GOLD A/B patients and 0.251 L for GOLD C/D patients.

For those with prior ICS use, trough FEV_1 was 0.160 L for GOLD A/B patients and 0.122 L for GOLD C/D patients receiving both tiotropium and olodaterol. For those with no prior ICS use, trough FEV_1 was 0.142 L for GOLD A/B patients and 0.149 L for GOLD C/D patients.

The TONADO studies included patients with moderate to very severe disease, but were conducted when the GOLD guidelines recommended that ICS plus LABA therapy be restricted to those with severe or very severe COPD and repeated exacerbations – before the guidelines were updated to take into account COPD symptoms.

The updated guidelines call for ICS plus LABA maintenance therapy for patients in categories C and D disease with frequent exacerbations.

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VITALS

Key clinical point: Inhaled corticosteroid plus long-acting beta$_2$-agonist therapy is overused in patients with mild COPD.

Major finding: Before study entry, 7.2% of GOLD A/B patients were receiving ICS and 31.1% were receiving ICS plus LABA; 8.8% of GOLD C/D patients were receiving ICS and and 45% were receiving ICS plus LABA.

Data source: A post hoc analysis of data for 5,162 patients from the phase III TONADO studies.

Disclosures: The study was supported by Boehringer Ingelheim, the maker of Respimat FDC.

Continued from previous page

older patients, and -7.3 in the younger patients, and the adjusted mean difference vs. placebo in change in Asthma Control Questionnaire scores from baseline to 32 weeks was -0.1 and -0.5 in the older and younger patients, respectively, he noted.

The older patients, as expected, suffered more frequently from comorbidities, and this may have been accentuated by the chronic use of inhaled and oral corticosteroids in the older patients.

However, comorbidities had no impact on the response to treatment, and the safety profile of mepolizumab was similar to placebo in both age groups, he said.

Patients in the multicenter, randomized, placebo-controlled MENSA trial received high dose inhaled corticosteroids plus at least one additional controller, had a history of frequent exacerbations and a predefined eosinophilic threshold, and were randomized to receive add-on therapy with either 75 mg of intravenous mepolizumab, 100 mg subcutaneous mepolizumab, or corresponding placebo every 4 weeks for 32 weeks.

In the primary planned analysis, the responses to the two doses of mepolizumab were similar, but efficacy in older patients had not been previously reported.

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Umeclidinium triple therapy improved lung function in COPD

BY SHARON WORCESTER
Frontline Medical News

DENVER – Lung function and health-related quality of life improved for COPD patients who received the long-acting muscarinic agent (LAMA) umeclidinium with fixed-dose inhaled corticosteroid/long-acting beta antagonist (LABA) therapy, based on a post hoc analysis of pooled data from four phase III trials.

Compared with inhaled corticosteroid (ICS)/LABA therapy alone, the triple therapy increased the number of rescue-free days, Dr. Thomas Siler, a pulmonologist with Midwest Chest Consultants, St. Charles, Mo., reported at an international conference of the American Thoracic Society.

The analysis involved 819 patients treated with 62.5 mcg of umeclidinium (Ellipta) – an approved maintenance treatment for COPD – plus ICS/LABA, 821 patients treated with 125 mg umeclidinium plus ICS/LABA, and 818 who received placebo and ICS/LABA. Statistically significant improvements were seen with active triple therapy vs. dual therapy plus placebo in forced expiratory volume in 1 second (FEV_1) at day 85 (0.130 L) and at all other time points, as well as in 0-6 h weighted mean FEV_1 at day 84 (0.152 L), Dr. Siler said.

With active triple therapy vs. dual therapy plus placebo, overall rescue use was reduced by 0.3 puffs/day and the number of rescue-free days increased by 7.1%. Also, St. George's Respiratory Questionnaire (SGRQ) score at day 84 decreased by 1.55 vs. placebo. The proportion of SGRQ responders was 41% vs. 31% for umeclidinium vs. placebo (odds ratio, 1.6).

Moderate/severe COPD exacerbations were experienced by 88 patients: 31 (4%) of the umeclidinium group patients and 57 (7%) of the placebo group patients (hazard ratio, 0.53).

The findings were similar in the patients who received off-label 125-mg dosing of umeclidinium, and the incidence of adverse events and serious adverse events was similar across treatment groups.

Data on the benefits of LAMAs in triple therapy in patients with moderate to very severe COPD are limited. This pooled analysis of data from four randomized, double-blind, parallel-group 12-week trials of once-daily add-on umeclidinium included COPD patients who entered a 4-week run-in on open-label ICS/LABA (either fluticasone furoate/vilanterol 100/25 mcg or fluticasone propionate/salmeterol 250/50 mcg), and who were then randomized to receive 62.5 or 125 mcg of umeclidinium or placebo. GlaxoSmithKline funded the study.

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CT-derived FFR may alter chest pain management

BY BRUCE JANCIN
Frontline Medical News

VITALS

Key clinical point: Clinically decisive anatomic and physiologic data regarding the coronary arteries of patients with stable angina can be obtained noninvasively with a single test: CT-derived fractional flow reserve.

Major finding: Noninvasive FFR-CT findings resulted in a change in management strategy for 36% of patients with stable angina whose initial treatment plan was based on CT angiography alone.

Data source: A proof-of-concept study involving 200 patients with stable angina and a panel of three experienced interventional cardiologists making consensus decisions regarding their appropriate management.

Disclosures: The FFR-CT RIPCORD study was sponsored by Heartflow. The presenter reported having received research support from the company.

PARIS – Noninvasive measurement of computed tomography–derived fractional flow reserve is a potential game changer in the management of patients with stable chest pain.

In a 200-patient proof-of-concept study known as FFR-CT RIPCORD, in which three experienced interventional cardiologists initially devised management plans based on coronary anatomy as defined by the results of CT angiography alone, subsequent knowledge of CT-derived fractional flow reserve (FFR-CT) caused them to change their management strategies in fully 36% of cases, Dr. Nick Curzen reported at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

"If this novel proof-of-concept result can be confirmed in large-scale trials, this suggests that noninvasive FFR-CT can be used as a clinically relevant tool that mimics the well-described ability of invasive FFR to refine management decisions for patients with chest pain that are made by invasive coronary angiography alone. This would indeed have implications for routine clinical practice. FFR-CT may have potential as a noninvasive default method for simultaneous assessment of coronary anatomy and physiology in angina patients in order to define their management, which would completely change the way we look after them," Dr. Curzen, professor of interventional cardiology at the University of Southampton (England), said.

EuroPCR codirector Dr. Williams Wijns was favorably impressed by the FFR-CT RIPCORD findings.

"This is a complete change in paradigm. Many patients that today undergo invasive angiography won't even be sent to the cath lab. The invasive center becomes only for treatment," commented Dr. Wijns, codirector of the cardiovascular center in Aalst, Belgium.

In FFR-CT RIPCORD, the cardiologists received information about a patient's history and nonvasive CT angiography findings and were asked to reach consensus in selecting one of four management options: optimal medical therapy (OMT) alone, PCI plus OMT, CABG surgery and OMT, or 'more information needed' in the form of FFR findings, which identify those coronary lesions that are actually causing ischemia. Instead of receiving the results of conventional invasive FFR obtained using a pressure wire, however, the cardiologists were provided with the noninvasive FFR-CT findings.

The resultant changes in management were substantial. Thirty percent of the patients initially slated for PCI were reallocated to OMT alone because no ischemic lesions were present; 12% of patients assigned to OMT-only got reassigned to coronary revascularization.

Moreover, in 18% of the PCI group, FFR-CT data led to a change in the vessel or vessels targeted for intervention.

"What particularly impressed me were two of those figures: that one-third of PCI patients are redirected to medical therapy, and – even more impressive to me – is the 18% of PCI patients who had a change in their target vessel. That's a problem we often have in patients with multivessel disease and intermediate lesions: Sometimes we think, for example, the target is the LAD when in fact it's another vessel," commented Dr. Jean Fajadet, codirector of the interventional cardiovascular group at the Clinique Pasteur in Toulouse, France.

FFR-CT could provide in one fell swoop a standardized way of obtaining both the anatomic and physiologic data necessary for informed clinical decision making, and without exposing patients to the risks of contrast and radiation exposure entailed in invasive coronary angiography.

"When we assess people with stable angina, if you have a room full of invasive cardiologists, we all do it differently ... It's a real mess. The thing I love about FFR-CT is it would be so slick for patients and their families: You see them in a chest pain clinic or your office and you put them in for this test. They don't have to waste their time coming back several times for different tests. It's a really beautiful concept," Dr. Curzen said.

A cost-effectiveness analysis of FFR-CT versus current standard care is ongoing and the results aren't yet available.

However, Dr. Curzen observed, "The cost to the patient is a very important issue: Who would want to have this done invasively if you have a test that proves you don't need to have an invasive procedure?"

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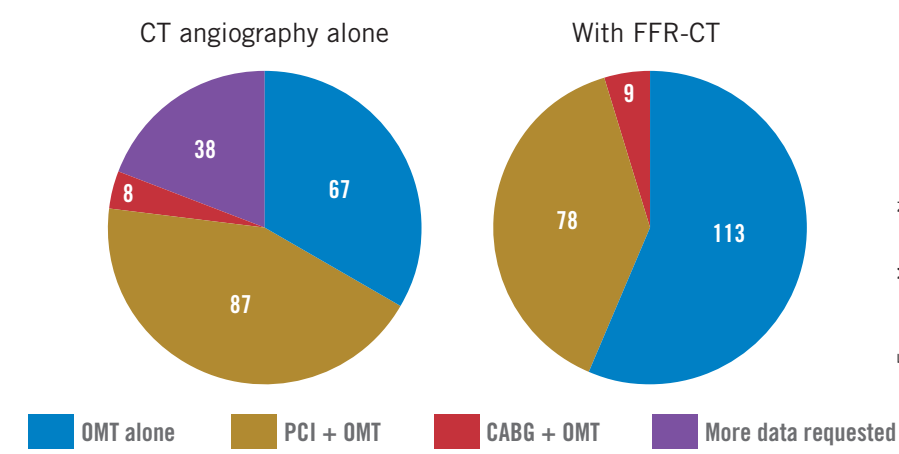
How FFR-CT altered management recommendations



Notes: The proof-of-concept study involved 200 patients, with a three-cardiologist panel reaching a consensus on appropriate management. "More data requested" = FFR-CT findings; OMT = optimal medical therapy.

Source: Dr. Curzen

Considering treatment options for your pulmonary arterial hypertension (PAH) patients?

REVATIO® (sildenafil)— is now available as an oral suspension treatment for PAH

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α–blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Consider REVATIO oral suspension for your appropriate PAH patients.
To learn more about REVATIO, please visit REVATIOHCP.com.

Please see brief summary of Full Prescribing Information on following pages.

Revatio® sildenafil **20 mg tablets**

RVU751722-02

June 2015

Revatio® sildenafil 20 mg tablets

Brief Summary of Prescribing Information. Consult Full Prescribing Information at REVATIOHCP.com

INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension *[see Warnings and Precautions]*, Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations]*.

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). 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.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications]*.

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only Rev. June 2015

Chest pain evaluation risk may outweigh benefit

BY MARY ANN MOON
Frontline Medical News

The chance that chest pain signals a cardiac event is "exceedingly low" – only 0.06% – in adults who have two negative results on troponin testing, nonconcerning vital signs, and nonischemic ECG findings in the emergency department, according to a report published in JAMA Internal Medicine.

To quantify the incidence of truly life-threatening cardiac events among patients admitted or observed for chest pain, Dr. Michael B. Weinstock of the department of emergency medicine, Ohio State University, Columbus, and his associates analyzed the medical records of 45,416 ED cases seen at three Midwestern hospitals during a 5-year period. Roughly half were admitted to an inpatient unit or an extended observation unit.

The study focused on the 7,266 patients who presented with chest pain, tightness, burning, or pressure, and who had negative results on serial troponin testing, normal vital signs, and normal ECG findings. Only four of these patients (0.06%) had a life-threatening outcome of interest: arrhythmia, ST-elevation myocardial infarction, cardiac or respiratory arrest, or death. Notably, one patient had a periprocedural MI and another had a STEMI during a stress test. A third patient, an 80-year-old man with coronary artery disease, hypertension, diabetes, obesity, chronic heart failure, chronic obstructive pulmonary disease, and renal failure, had noncardiac chest pain from massive GI bleeding secondary to warfarin coagulopathy. And a woman with hypertension, CAD, and a coronary artery bypass graft developed bradyasystolic cardiac arrest when given nitroglycerin, the investigators said (JAMA Intern. Med. 2015 May 18 [doi:10.1001/jamainternmed.2015.1674]).

"Our findings support the notion that adverse iatrogenic events as a result of admission may eclipse potential benefits" in chest pain patients who are at low risk for a cardiac event," they said.

VITALS

Key clinical point: The chance that chest pain signals a cardiac event is "exceedingly low" in ED patients who have negative serial biomarker results, nonconcerning vital signs, and nonischemic ECG findings.

Major finding: Only 4 of the 7,266 patients (0.06%) who presented with chest pain, tightness, burning, or pressure, and who had negative results on serial troponin testing, normal vital signs, and normal ECG findings, had a life-threatening cardiac event.

Data source: An analysis of the medical records of 45,416 adults admitted or observed for chest pain at three Midwestern hospitals during a 5-year period.

Disclosures: Dr. Weinstock had no relevant disclosures; two of his associates reported ties to AstraZeneca and Callibra.

VIEW ON THE NEWS

Cognitive biases in testing

The findings of Weinstock et al. are consistent with our own results from focus groups of internists and cardiologists: Physicians often anticipate they'll regret missing a cardiac diagnosis and reflexively value taking some action over inaction, cognitive biases that ultimately lead to unnecessary testing and invasive treatment of patients with chest pain.

For their part, patients also greatly overestimate the benefits of tests and treatments while greatly underestimating their risks. Given accurate and complete information about harms and benefits of certain interventions, many chest pain patients would make different choices.

Grace A. Lin, M.D., is in the department of medicine at the University of California, San Francisco, Philip R. Lee Institute for Health Policy Studies. Rita F. Redberg, M.D., is professor and director of women's cardiovascular services at University of California, San Francisco, and is chief editor of JAMA Internal Medicine. Dr. Lin and Dr. Redberg reported having no financial conflicts of interest. They made these remarks in an editorial accompanying Dr. Weinstock's report (JAMA Intern. Med. 2015 May 18 [doi:10.1001/jamainternmed.2015.1693]).

FDA approves IV antiplatelet drug cangrelor

BY MITCHEL L. ZOLER
Frontline Medical News

Cangrelor became the first intravenous antiplatelet agent acting on ADP receptors for adult patients undergoing percutaneous coronary intervention to receive marketing approval from the Food and Drug Administration, The Medicines Company announced.

While cangrelor's unique delivery route and rapid onset and off-set of action set it apart and may give it certain clinical advantages over the three approved oral drugs that target the same platelet receptor – clopidogrel, prasugrel (Effient), and ticagrelor (Brilinta) – cangrelor will also be distinguished by its much higher price. The standard dosage to treat one patient undergoing percutaneous coronary intervention (PCI) with cangrelor (Kengreal) will have a wholesale acquisition cost of $749, Raymond Russo, senior vice president of The Medicines Company, said at a June 23 press briefing. That prices cangrelor substantially above its brand-name competition, which costs roughly $25 for similar treatment, as well as generic clopidogrel, which costs about $3 for the same indication.

"I believe in the strength of the data that showed that cangrelor was superior to the comparator drug [clopidogrel], and if cost were not an issue I'd use cangrelor routinely, but I am not naive; cost is an issue," said Dr. Deepak L. Bhatt, professor of medicine at Harvard University and executive director of interventional cardiology programs at Brigham and Women's Hospital in Boston, and co–lead investigator for the CHAMPION PHOENIX pivotal trial that led to cangrelor's approval (N. Engl. J. Med. 2013;368:1303-13).

Whether or not interventional cardiologists and the centers where they work decide to use cangrelor or one of the oral antiplatelet drugs for coronary artery disease (CAD) patients undergoing PCI will likely depend on a series of considerations that will need to take into account not just drug cost but also practice strategies, a patient's clinical state, and the potential for ancillary costs from following an entirely different management approach.

The first issue is whether the interventionalist decides to pretreat a patient scheduled for angioplasty and possible immediate PCI following angiography with an ADP-receptor antagonist (also known as a P2Y*12*-receptor inhibitor) prior to the start of angiography or opts to defer that treatment until the angiography results are available and a decision is made to proceed with PCI.

The expense of waiting for an ADP-receptor antagonist to clear could be obviated by cangrelor.

DR. BHATT

Recent nationwide registry data suggest that roughly half of U.S. interventionalists treat their patients upfront with an ADP-receptor antagonist, usually clopidogrel for patients with stable angina or prasugrel or ticagrelor if they have either a non-ST-elevation MI or a ST-elevation MI, while the other 50% of interventionalists will wait to administer the ADP-receptor antagonist until angiography is complete, Dr. Bhatt explained in an interview.

The advantage to upfront treatment is that by the time the patient is ready for PCI an oral ADP-receptor antagonist is fully absorbed and on board. The disadvantage is that if the coronary anatomy demands a surgical approach to revascularization many surgeons would elect not to operate on a patient freshly dosed with an antiplatelet agent, and these patients often remain hospitalized for several days until the ADP-receptor antagonist clears and the patient's platelet function returns to normal. Angiography generally identifies 10%-15% of these patients with a CAD distribution that necessitates surgical coronary bypass, and the potential hospitalization expense of waiting for their ADP-receptor antagonist to clear could be a major cost to counterbalance the price of cangrelor, which would obviate this expense if the quick-to-start-and-to-clear cangrelor were used instead of a more lumbering oral drug, he noted.

The other 50% of U.S. interventionalists, Dr. Bhatt included, take a different approach. Recognizing the potential downside of upfront oral antiplatelet therapy if the patient is pegged for bypass surgery following angiography, they elect to wait until the angiography results are in hand. If the angiography results show the patient is destined for surgery or for medical management, then the patient receives no ADP-receptor antagonist. The cardiologist administers an ADP-receptor antagonist only if the patient's CAD is appropriate for PCI, the fate for most of these CAD patients following angiography. It's under these circumstances that the advantages of cangrelor kick in, as shown in CHAMPION PHOENIX.

This trial randomized patients to two different types of ADP-receptor antagonist treatment while they were in the coronary catheterization laboratory. The study results showed a statistically significant, 22% relative-risk reduction in the primary endpoint in favor of intravenous cangrelor compared with oral clopidogrel delivered while patients were "on the table" in the interval between angiography and PCI. That 22% relative improvement in outcomes, driven primarily by reductions in periprocedural MIs and stent thrombosis, improved to a 31% relative-risk reduction when The Medicines Company performed a new analysis of the study results at the FDA's request using a more stringent and conventional definition of periprocedural MIs and stent thrombosis. The time needed to perform this and other FDA-requested analyses largely caused the greater than 2-year gap between the 2013 publication of the CHAMPION PHOENIX results and the FDA's approval.

But the editorial that accompanied the 2013 publication highlighted what the editorialists perceived as flaws in the study's design, such as an inadequate loading dose of clopidogrel delivered to a quarter of the patients randomized to that arm, inadequate time allowed for the clopidogrel to fully kick in before PCI began in a third of patients, and the use of clopidogrel as the comparator drug and not a more potent alternative drug, either prasugrel or ticagrelor (N. Engl. J. Med. 2013;368:1356-7).

"Cangrelor was never tested against prasugrel or ticagrelor, and it was compared with inadequate clopidogrel treatment. That was a problem," reiterated Dr. Richard A. Lange, one of the 2013 editorialists, when interviewed following news of cangrelor's FDA approval.

CHAMPION PHOENIX "wasn't really a comparison [of two drugs], it was a study of an intravenous strategy, and it's not a strategy that is needed very often," said Dr. Lange, an interventional cardiologist and president of the Texas Tech University Health Sciences Center in El Paso. In Dr. Lange's opinion, the only real need for an intravenous ADP-receptor antagonist is for CAD patients undergoing PCI who are unable to take an oral agent, for example because they are on a ventilator, unable to hold down an oral pill, or unconscious, which collectively are "rare" situations, he said.

Dr. Bhatt noted that another clear indication for an intravenous agent is when MI patients receive morphine for their pain, a situation recently documented to interfere with absorption of oral ADP-receptor antagonists.

CHAMPION PHOENIX "wasn't really a comparison [of two drugs], it was a study of an intravenous strategy, and it's not a strategy that is needed very often.

From Dr. Bhatt's perspective, the major issue is practice patterns: "Do the interventionalists treat [with an ADP-receptor antagonist] upstream or not. If they do, then they should do the math," and determine if the expense of holding a significant minority of patients in the hospital just to allow them to clear the ADP-receptor antagonist prior to coronary bypass surgery outweighs the cost for delaying this treatment and administering cangrelor later only to patients scheduled for PCI. At the center where he practices, Brigham and Women's Hospital in Boston, he sees a roughly equal mix of interventionalists who prefer to treat patients with clopidogrel upfront, those who treat with ticagrelor upfront, and those who practice as he does and wait until the PCI is a go.

"For my personal practice, cangrelor will fit in quite nicely," Dr. Bhatt said.

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Warfarin bridge ups bleeds, with no drop in VTEs

BY BIANCA NOGRADY
Frontline Medical News

Bridge therapy for warfarin patients undergoing invasive therapy is unnecessary for most patients, said investigators who found an increased risk of bleeding associated with the use of the short-acting anticoagulant at the time of the procedure.

A retrospective cohort study of 1,812 procedures in 1,178 patients – most of whom were considered to be at low risk of venous thromboembolism recurrence – showed a 17-fold increase in the risk of clinically relevant bleeding in the group that received bridge anticoagulant therapy, compared with the group that didn't (2.7% vs. 0.2%).

There was, however, no significant difference in the rate of recurrent venous thromboembolism between the bridge-therapy and non–bridge-therapy groups (0 vs. 3), and no deaths were observed in either group, according to an article published online (JAMA Intern. Med. [doi:10.1001/jamainternmed.2015.1843].

"Our results confirm and strengthen the findings of those previous studies and highlight the need for a risk categorization scheme that identifies patients at highest risk for recurrent VTE who may benefit from bridge therapy," wrote Thomas Delate, Ph.D., from Kaiser Permanente Colorado, and coauthors.

The study was conducted and supported by Kaiser Permanente Colorado.

One author reported consultancies with Astra-Zeneca, Boehringer-Ingelheim, Pfizer, and Sanofi.

VIEW ON THE NEWS

Reserve for the high-risk patient

There are undoubtedly some patients at such high risk for recurrent venous thromboembolism that bridge therapy is a necessary evil, such as those with acute VTE in the preceding month and those with a prior pattern of brisk VTE recurrence during short-term interruption of anticoagulation therapy.

However, for the vast majority of patients receiving oral anticoagulants for VTE, it is probably safer to simply allow the oral anticoagulant to wash out before the procedure and, if indicated based on the type of surgery, to use routine prophylactic-dose anticoagulation therapy afterward.

Dr. Daniel J. Brotman and Dr. Michael B. Streiff are from Johns Hopkins University, Baltimore. These comments are taken from an accompanying editorial (JAMA Intern. Med. 2015 May 26 [doi:10.1001/jamainternmed.2015.1858]). Dr Streiff declared research funding from Bristol-Myers Squibb and Portola and consultancies for Boehringer-Ingelheim, Daiichi-Sankyo, Eisai, Janssen HealthCare, Pfizer, and Sanofi.

High-flow oxygen for hypoxemic respiratory failure

BY MARY ANN MOON
Frontline Medical News

High-flow oxygen delivered via nasal cannula significantly decreased mortality and improved comfort for ICU patients with nonhypercapnic acute hypoxemic respiratory failure, according to a report published in the New England Journal of Medicine.

High-flow oxygen didn't reduce endotracheal 1-month intubation rates, however, as compared with standard oxygen delivery or noninvasive ventilation in a prospective randomized controlled trial comparing the three techniques at 23 ICUs across France and Belgium, said Dr. Jean-Pierre Frat of Centre Hospitalier Universitaire de Poitiers (France) and his associates.

The 2-year study included 310 adults with nonhypercapnic acute

hypoxemic respiratory failure, which was usually the result of community-acquired pneumonia.

Patients were randomly assigned to receive high-flow oxygen delivered continuously through large-bore nasal prongs (106 patients), standard oxygen therapy delivered continuously through a nonrebreather face mask (94 patients), or noninvasive ventilation delivered through a face mask connected to an ICU ventilator (110 patients).

Intubation rates at 30 days were 38% for high-flow oxygen, 47% for standard oxygen, and 50% for noninvasive ventilation, which are nonsignificant differences.

The hazard ratio for death at 90 days was 2.01 for standard oxygen and 2.5 for noninvasive ventilation, as compared with high-flow oxygen.

Additionally, the number of ventilator-free days at 1 month was significantly greater with high-flow oxygen (24 days) than with either of the other techniques (22 days and 19 days, respectively), the researchers said.

High-flow oxygen also reduced the intensity of respiratory discomfort at 1 hour to a significantly greater degree than did either of the other forms of oxygen delivery and decreased the dyspnea score as well.

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"These findings might result from the heating and humidification of inspired gases, which prevented thick secretions and subsequent atelectasis, but also from low levels of PEEP [positive end-expiratory pressure] generated by a high gas flow rate and flushing of upper-airway dead space," they added (N. Engl. J. Med. 2015 June 4 [doi:10.1056/NEJMoa1503326]).

The hazard ratio for death at 90 days was 2.01 for standard oxygen and 2.5 for noninvasive ventilation, as compared with high-flow oxygen.

Rates of complications were similar among the three study groups.

The study was supported by the French Ministry of Health's Programme Hospitalier de Recherche Clinique Interregional 2010.

Dr. Frat reported receiving travel fees from Fisher & Paykel Healthcare and personal fees from SOS Oxygene.

Fisher & Paykel Healthcare donated face masks, heated humidifiers, and cannulas and provided air-oxygen blenders to the participating ICUs.

Radiation added no benefit after pneumonectomy

BY M. ALEXANDER OTTO
Frontline Medical News

SEATTLE – Adding radiotherapy to neoadjuvant chemotherapy does not improve long-term survival after pneumonectomy for non–small cell lung cancer, according to a Turkish investigation of 140 patients.

In the study, 100 (71.4%) patients had two to six cycles of platinum-based chemotherapy at least 3 weeks before surgery; 40 (28.6%) others underwent the same regimen with the addition of radiotherapy dosed at 45-66 Gy 6-8 weeks before surgery.

Five-year survival was 48% in the chemotherapy group and 50% in the chemoradiation group, an insignificant difference ($P = .7$).

"Chemotherapy before surgery is definitely beneficial, but I think we will get rid of the radiotherapy" in

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patients with operable tumors, said lead investigator Dr. Cengiz Gebitekin, professor and head of thoracic surgery at Uludag University in Bursa, Turkey.

"It does not provide any survival benefit," and it might cause harm, he noted, adding that "the benefit of neoadjuvant treatment comes from the chemotherapy."

The chemoradiation group showed a tendency toward tumor down-staging and higher complete response rates, but also a trend toward more radiation-induced tissue damage. The rate of bronchopleural fistula was 3% in the chemotherapy group and 5% in the chemoradiation group, although the difference was not significant. Even so, "some of these patients had pneumonectomies because of lung damage from the radiotherapy," Dr. Gebitekin said at the annual meeting of the American Association for Thoracic Surgery.

It's uncertain why radiation didn't improve survival. The investigators excluded patients with known metastases or other malignancies, but it's possible that some patients had occult metastases that had spread beyond the field of their localized neoadjuvant radiation, he said.

The patients were treated between 2000 and 2013 at Uludag University, Istanbul University, and Zurich University Hospital. They were 55 years old on average, and 84% were men.

About 40% of patients in both the chemotherapy and chemoradiation groups had right pneumonectomies; the rest had left pneumonectomies. Bronchopleural fistulas and other comorbidities were more common after right pneumonectomies, but not significantly so.

Seven patients (5%) in the chemotherapy group but none in the chemoradiation group died within 90 days of surgery.

About 32% of chemotherapy patients and 28% of chemoradiation patients ($P = .6$) developed major morbidities following surgery, including arrhythmias, pneumonia, empyema, and other problems.

The chemoradiation group had a trend toward more radiation-induced tissue damage.

DR. GEBITEKIN

Staples were used to close the bronchus in almost all patients, with the stump covered with live tissue in about 70%.

The majority of patients had stage IIb or IIIa disease on postop staging; postop staging was the only factor predictive of long-term survival, with higher-stage patients doing worse.

Dr. Gebitekin said that he had no relevant disclosures.

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VITALS

Key clinical point: Limit neoadjuvant treatment to chemotherapy for non–small cell lung cancer patients.

Major finding: About half of patients were alive 5 years after pneumonectomies for lung cancer, whether they had neoadjuvant chemotherapy or chemoradiation.

Data source: Retrospective study of 140 pneumonectomy patients.

Disclosures: Dr. Gebitekin had no disclosures.

High-dose nitric oxide promising in bronchiolitis

BY DOUG BRUNK
Frontline Medical News

DENVER – Intermittent high-dose nitric oxide (NO) inhalation therapy appears safe and shows clear signals of efficacy in infants hospitalized with bronchiolitis, a randomized controlled trial showed.

"Further larger scale clinical trials are needed to establish its role in lower respiratory tract infections such as viral bronchiolitis, pneumonia, cystic fibrosis, viral-related asthma, COPD [chronic obstructive pulmonary disease], and more," one of the study authors, Yossef Av-Gay, Ph.D., said in an interview in advance of an international conference of the American Thoracic Society.

In what they said is the first human study of its kind, researchers led by Dr. Asher Tal, head of the pediatric pulmonary unit at Soroka University Medical Center, Beer Sheva, Israel, set out to determine the safety and tolerability of intermittent high-dose inhaled NO for the treatment of hospitalized infants aged 2-12 months with bronchiolitis. Patients received either 160 parts per million (ppm) of NO five times per day for 30 minutes each time or oxygen only.

"Nitric oxide gas is used to treat neonates at lower dose, and in this study we investigated its antimicrobial dosage, which is higher than current treatment," said Dr. Av-Gay, professor of the division of infectious diseases at the University of British Columbia, Vancouver.

VITALS

Key clinical point: Intermittent high-dose inhaled nitric oxide was safe and shows signals of efficacy in infants with acute bronchiolitis.

Major finding: Infants who received nitric oxide spent significantly fewer hours in the hospital, compared with the oxygen group (a mean of 46 hours vs. 74 hours, respectively; P = .032) and reached 92% oxygen saturation in significantly less time (a mean of 26 hours vs. 61 hours; P = .032).

Data source: A randomized study of 25 infants with bronchiolitis who were hospitalized for more than 24 hours.

Disclosures: The study was funded by Advanced Inhalation Therapies, an Israeli-based company that holds the rights to the nitric oxide technology. Dr. Av-Gay is the company's chief scientific officer, and Dr. Tal is employed by the company.

"Previous in-vitro and in animal studies support the antimicrobial effect of intermittent inhalations of 160 ppm of NO to treat lower respiratory tract infections, both viral and bacterial. Bronchiolitis is a viral-related [infection] that causes significant morbidity and even mortality in infants around the world. Presently the treatment protocol for hospitalized infants is supportive care only, because despite many years of research as there is not yet an available treatment or specific anti-viral drug. Inhaled NO is thus an exciting potential novel drug for the treatment of acute bronchiolitis," he said.

Of 43 infants initially enrolled, 25 were hospitalized for more than 24 hours and were considered evaluable for efficacy. Of these, 14 received intermittent high-dose inhaled NO and 11 received oxygen only. The researchers observed no significant differences between the NO and oxygen groups in the number of adverse events or in the number of serious adverse events. Patients who received NO, however, spent significantly fewer hours in the hospital, compared with the oxygen group (mean of 46 hours vs. 74 hours, respectively; $P = .032$) and reached 92% oxygen saturation in significantly faster time (mean of 26 hours vs. 61 hours; $P = .032$).

Dr. Av-Gay acknowledged certain limitations of the analysis, including the fact that the study's primary outcome was safety and tolerability. "Therefore, the study was not powered to show efficacy," he said.

The study was funded by Advanced Inhalation Therapies, an Israeli-based company that holds the rights to the NO technology. Dr. Av-Gay is the company's chief scientific officer, and Dr. Tal is employed by the company.

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Guidelines can decrease hospital costs for bronchiolitis

BY DEEPAK CHITNIS
Frontline Medical News

SAN DIEGO – Implementation of guidelines for the use of the high-flow nasal cannula in general pediatric wards for infants admitted with bronchiolitis can lead to significant decreases in length of stay, need for ICU level of care, and overall hospitalization costs, a retrospective chart study showed.

In the nonrandomized, pre- and postintervention chart analysis, the investigators reviewed the data for 2,446 infants under age 2 years who were admitted to Hasbro Children's Hospital for bronchiolitis in the 24 months before and after March 2012, when the hospital initiated high-flow nasal cannula (HFNC) protocols in its general pediatric wards.

"Admissions for bronchiolitis are extremely common for children under the age of 1 [year], and the costs associated with this are obviously quite high, but although centers around the country are now using [HFNC] for bronchiolitis, there's little data at this point regarding the use of it on the general wards," said Dr. Jamie Fierce of Hasbro Children's Hospital in Providence, R.I., adding that the 2014 American Academy of Pediatrics guidelines on bronchiolitis called for more research on the efficacy of HFNC (Pediatrics 2014;134:e1474-502).

VITALS

Key clinical point: Implementing guidelines for the use of a high-flow nasal cannula for babies with bronchiolitis in a general pediatric hospital ward was associated with decreases in length of stay, need for admittance to an ICU, and hospitalization costs.

Major finding: Median length of stay decreased from 4 days to 3 days (*P* less than .001), the proportion of bronchiolitis patients who spent any time in the ICU decreased from 100% to 70% (*P* less than .001), and the median hospitalization costs decreased from $12,865 to $8,952 (*P* less than .001).

Data source: A retrospective chart study of 533 children under the age of 2 years, for 24 months before and after implementation of HFNC in general pediatric wards at Hasbro Children's Hospital.

Disclosures: Dr. Fierce did not report any relevant financial disclosures.

In total, 533 infants were selected for the study, and were divided into groups based on whether they were admitted and discharged before or after the March 2012 implementation of HFNC protocols. The primary outcome was the length of hospital stay; the median length before implementation was 4 days, which decreased to 3 days after implementation (*P* less than .001). In addition, the number of patients who required an ICU level of care decreased from the mandated 100% – because every subject who received HFNC would have to be admitted to the ICU before the new protocols were in place – to 70% after the new protocols were put in place (*P* less than .001).

The cost of hospitalization also decreased significantly; prior to HFNC use on general wards, the median cost per patient was $12,865, but that amount decreased to $8,952 after March 2012, a difference of almost $4,000. Furthermore, there was no increase in intubation rates, nor in 30-day readmission rates from before to after March 2012. The average number of days spent on HFNC dropped from 2.5 days to 2 days, and the mean maximum HFNC rate also decreased from 9 L/min to 7 L/min, Dr. Fierce said at the annual meeting of the Pediatric Academic Societies.

"One important limitation to this study is that it's difficult to assess bronchiolitis severity in each of our groups, so there could have been seasonal variations that may have affected our outcomes," he said. "Our after-implementation group is larger than our before-implementation group, and it's hard to tell if that's due to a seasonal increase in bronchiolitis cases, or if there was just higher use of HFNC on patients once it was allowed in the general wards."

The median cost of hospitalization per patient dropped from $12,865 to $8,952 after the introduction of high-flow nasal cannula protocols.

Although there was a statistically significant difference in age between the groups – 3 months before March 2012, 5 months after – the other demographic data were largely consistent.

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FROM THE EVP/CEO: Aligning for the future with trainees

PAUL A. MARKOWSKI, CAE
Executive Vice President/CEO, CHEST

CHEST is fortunate to have a history of dedicated leaders committed to advancing patient care and chest medicine. Our Past Presidents and leaders have guided us through the relevant developments in chest medicine to position us as a strategic leader in the field, and our current leaders continue doing the same. An important role our leaders have always played is mentoring the next generation—our physicians-in-training. Recognizing they are the future lifeblood of CHEST, we offer them personal and professional growth opportunities to advance their careers and get more involved with CHEST.

One of our newer opportunities, made available this May, is CHEST membership. It's now open to the entire chest team, including all trainees—fellows, residents, interns, medical students, and other clinicians-in-training. Three levels of membership offer a range of benefits, so trainees, or any member, can decide which category best suits their needs, expectations, and preferences. To help make membership more accessible, trainees are given a $200 discount off their chosen level. We've already welcomed a few dozen students and residents into membership this past month, and we're watching that number grow.


MR. MARKOWSKI

We want to do more than attract trainees to CHEST; we want to offer them useful tools to help them through the various stages of their training and careers. Our Training and Transitions Committee is finishing up work on a new "Trainee Resources Hub." Expected to launch the end of this month, the hub will be available at chestnet.org and will include tips, tricks, resources, blog posts about various career stages, and links to additional resources. There will be a general information page, as well as pages for medical students/residents, fellows, and those transitioning out of fellowship. The hub will be a great source for practical information. Be sure to look for it later this month.

The CHEST Annual Meeting is the ideal place for trainees to network with other professionals in their specialties, so we offer plenty of opportunities for them to make connections.

CHEST 2015 will feature a Trainee Lounge, to be open the afternoons of Sunday, October 25, to Tuesday, October 27. While plans for specific programming are still under development, trainees can expect informal presentations on topics relevant to their career stages, networking opportunities with leadership, as well as comfortable seating and snacks when it's time for a break.

Plans are also underway for our 22nd Pulmonary and Critical Care Fellows Conference (available by invitation only), the Trainee and NetWorks Mixer, and the always popular CHEST Challenge Championship. The Training and Transition Committee will provide a list of recommended sessions trainees will want to check out during the course of the meeting.

Look for more information about CHEST 2015 features on chestmeeting.chestnet.org, and watch your mailboxes in August for the CHEST 2015 advance program and *CHEST Daily News* (newspaper) preview issue.

It's important that CHEST be aligned to continue moving forward strategically. When we take these steps to involve and mentor our next generation, we're aligning ourselves for success.

CHEST membership is now open to the entire chest medicine team, including all trainees – fellows, residents, interns, medical students, and other clinicians-in-training.

I welcome your input on how we can continue advancing our trainees' careers, and I welcome your involvement to make it happen. As always, feel free to connect with me to share your ideas. I invite you to follow me on Twitter, @PMarkowskiACCP, or look for me at upcoming CHEST events.

1-Day registration for CHEST 2015: Come for the day or make a weekend of it

If you'd like to attend the CHEST Annual Meeting 2015 but have trouble scheduling time away from your practice, consider the 1-day registration. Register for any given day, Sunday through Wednesday. Or, attend for the weekend by registering for a postgraduate course on Saturday and 1 day on Sunday. If you come for the weekend, consider bringing your family. You won't be alone—there's so much to do for everyone in Montréal.

Postgraduate Courses

Saturday, October 24

Attend a postgraduate course for an intensive learning experience. Postgraduate courses include:

- A Case-Based Review of Cutting-Edge Critical Care: What's Happened Since You Left Fellowship?
- Advanced Critical Care Echocardiography
- Cardiopulmonary Exercise Testing 2015: An Evidence- and Case-Based Update
- Pulmonary Medicine 2015: Year in Review and Clinical Update
- Sleep Medicine 2015: Year in Review and Clinical Update

Program Highlights

CHEST 2015 is your connection to focused clinical education that will help optimize your patient care. The relevant sessions and community of innovative problem-solvers in attendance will be sure to inspire and energize you and your career. Don't miss these highlights:

Interdisciplinary Programs

Bring your entire care team to attend programs that will address clinical issues across the disciplines. Session speakers will represent each role and present from their perspective, so your group can collectively experience practical, relevant updates. Sessions will combine lecture-based, case-based, and hands-on learning opportunities.

CHEST Simulation Center

Practice your clinical skills in a hands-on learning environment. Work with expert faculty to sharpen your skills and apply your knowledge using real equipment and simulators.

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General Sessions

Choose from hundreds of sessions, offered in a variety of instructional formats, including hands-on simulation, interactive case-based presentations, small-group discussions, and a rich variety of self-study modules and educational games.

Exhibit Hall

Don't miss the showcase of diagnostic and treatment solutions for optimal patient care.

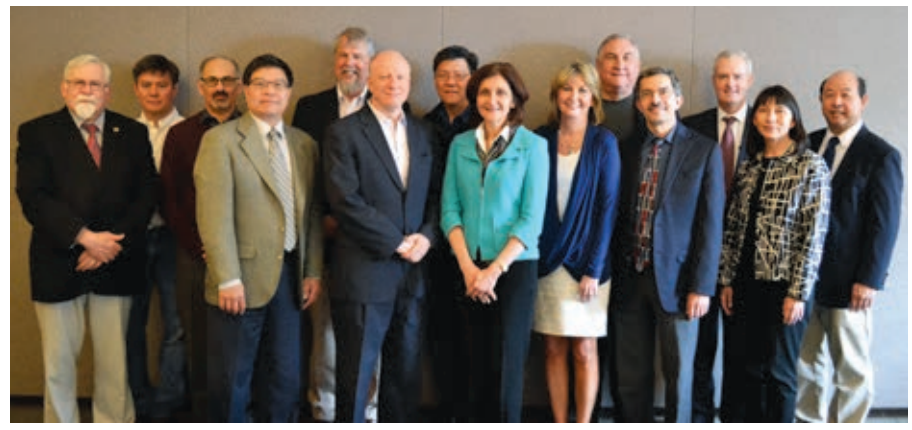
Explore Montréal!

Montréal is known for its warm camaraderie and joie de vivre! You'll enjoy this friendly city—a melting pot of ethnicities, languages, cuisines, and ideas. Explore Montréal's history in Old Montréal, take in a hockey game at the Bell Centre, breathe in the fresh air at Mount Royal, or enjoy a wide variety of classic Montréal foods. During your free time at CHEST 2015, you'll want to check out everything that Montréal has to offer.

Learn more about Montréal at tourisme-montreal.org, and find information about CHEST 2015 at chestmeeting.chestnet.org.

ABIM incorporates diplomate recommendations into MOC program

BY SERPIL C. ERZURUM, MD, FCCP
For the ABIM Pulmonary Disease Board



Members of ABIM's Pulmonary Disease Board and Pulmonary Disease Board Exam Committee (L-R): Dean Hess, PhD, FCCP; David E. Ost, MD, FCCP; Peter H. S. Sporn, MD, FCCP; Kevin M. Chan, MD, FCCP; John Allen Cooper, MD; Charles W. Atwood, MD, FCCP

We wanted to provide the pulmonary disease community with an update on the work ABIM has been doing to transform and improve its Maintenance of Certification (MOC) program. Recently, the Pulmonary Disease Board and Pulmonary Disease Board Exam Committee held a joint meeting in Philadelphia to discuss their roles in ensuring we continue to work closely with the physician community to enhance the MOC program, including the exam.

An important part of the work ABIM as a whole is undertaking is listening to the community so that it can design an MOC program that physicians find more meaningful and relevant. Tangible expressions of this listening are evident in the significant program changes announced by ABIM's Board of Directors.

A few of the changes, among the others announced, include:

• **Recognizing more activities for MOC credit.** In an effort to better link MOC with activities that physicians are already doing to stay current, by the end of 2015, ABIM will begin to accept a wider variety of approved CME activities for MOC points and streamline the process for its medical society partners to submit new activities. ABIM is interested in finding ways to recognize meaningful clinical work that you do in your practices to earn CME credit and is particularly interested in recognizing CME activities for which there is evidence that they drive learning and/or change practice.

• **New exam Score Report.** Results of all examinations beginning with the spring 2015 MOC exam administration will be released in a new, electronic format. For years, ABIM has heard that diplomates want more specific feedback on exam performance. The new Score Report was redesigned and created with the feedback and guidance of ABIM board-certified physicians, including many members of ABIM governance and community physicians. This collaboration led ABIM to the design of a new Score Report, which offers:

• Clearer graphical explanations of exam performance

• More detailed feedback on questions missed

• Less technical jargon in explaining the report

• Links to more in-depth information on the ABIM website

• **Updates to the Internal Medicine MOC exam blueprint.** Over the past 4 months, the Internal Medicine Board, the Internal Medicine Board Exam Committee, and ABIM staff worked with a representative sample of practicing general internists to review and update the IM MOC exam blueprint. Internists rated blueprint topics for frequency in practice and rated the relative importance of tasks (eg, diagnosis) performed in relation to each of those topics. Their ratings will now inform the exam assembly process for the fall 2015 IM MOC exam. This process will be used in the future for other disciplines, including pulmonary disease.

We encourage you to visit the Transforming ABIM blog to view sample pages from the new Score Report, learn more about how ABIM collaborated with physicians to update the internal medicine MOC exam blueprint, and read further about how ABIM came to the decision to change its website reporting language. In addition to the information on the exam Score Report and new blueprint, the blog also provides updates about ABIM's ongoing discussions with the community, upcoming opportunities to provide input, and more information regarding the changes mentioned above. Subscribe to the blog.

Another way ABIM is collaborating with the physician community is through Assessment 2020, a task force commissioned by the ABIM Board of Directors to develop a vision for the future of assessment for certification (initial and maintenance) in internal medicine and associated subspecialties. The task force comprises experts with diverse areas of expertise including assessment, medicine, health policy, education, and technology. Visit the site to learn more about how Assessment 2020 is engaging clinicians, patients, and other important members of the community to provide feedback on the skills physicians need to deliver the highest quality of care. Additionally, read how ABIM is putting this feedback into action as we look for ways to innovate and enhance the exam experience.

Also, as you might be aware, earlier this year, ABIM suspended the Practice Assessment, Patient Voice, and Patient Safety requirements for at least 2 years. This means that physicians participating in the MOC program are not required to complete these requirements but should still work toward completing the existing Medical Knowledge and MOC exam requirements for their certifications. To learn more about your specific requirements and deadlines, log into www.abim.org to view your MOC Status Report.

We look forward to sharing more updates with you as we continue our work of ensuring the relevancy of MOC to pulmonary disease physicians across the country.

This Month in *CHEST:* Editor's Picks

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

The Role for Optical Density in Heparin-Induced Thrombocytopenia: A Cohort Study. By Dr. C. M. Chan et al.

Standardizing Predicted Body Weight Equations for Mechanical Ventilation Tidal Volume Settings. By Dr. O. Linares-Perdomo et al.

Pneumonia Pathogen Characterization Is an Independent Determinant of Hospital Readmission. By Dr. A. Andruska et al.

Secondhand Smoking Is Associated With Vascular Inflammation. By Dr. T. Adams et al.

Assessment of Intervention Fidelity and Recommendations for Researchers Conducting Studies on the Diagnosis and Treatment of Chronic Cough in the Adult: CHEST Guideline and Expert Panel Report. By Dr. C. T. French; Ms. R. L. Diekemper; and Dr. R. S. Irwin; on behalf of the CHEST Expert Cough Panel.

Somatic Cough Syndrome (Previously Referred to as Psychogenic Cough) and Tic Cough (Previously Referred to as Habit Cough) in Adults and Children: CHEST Guideline and Expert Panel Report. By Dr. A. E. Vertigan; Dr. M. H. Murad; and Dr. T. Pringsheim; on behalf of the CHEST Expert Cough Panel.

Catching up with our Past Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to give us a look at what's new in their lives.

EDWARD C. ROSENOW III, MD, MS, MASTER FCCP President 1989-1990

It is a privilege and an honor to be asked to reminisce about my life experiences after my year as president of the College. I think we accomplished a lot during that year, with the completion of the new American College of Chest Physicians' headquarters in Northbrook and the College's participation in effecting the ban on smoking on domestic airline flights.

I retired in 1996 but continued to be very active in teaching and writing as I still am. Mayo's emeritus center is right in the middle of the campus that I go to three or four mornings a week; this keeps me in touch with a number of friends, encountering many of them regularly.

I go to lunch several times a week with old friends, as well as with pre-med students, fellows, my former secretary, and allied health personnel that I worked with for decades. One group comprises pulmonary colleagues that I have worked with for 4 decades.

I would urge my fellow retirees to do the same. It will help you stay 'young'! And you have to get out of the house, even in cold winter months. I teach year 2 medical students in their clinic at the Salvation Army. One of my greatest pleasures is mentoring pre-med students as well as residents/fellows and even young staff. Try it, you'll love it

I am working on my fourth book, and this is very stimulating. My first one was self-published in 2006 and titled *The Art of Living….The Art of Medicine*. This was followed by a 900+ slide compilation on a CD titled *Mayo Clinic Challenging Images for Pulmonary Board Review*. I'm currently working on two more: *The Interpretation of CXRs by a Nonradiologist*—this will be for primary care physicians and even nurse primary care providers. Hopefully, Mayo will publish this on to our education website. It is currently also being translated into Mandarin.

Finally, one that only an old man could write, and that is *The Making of the Physician*, beginning with the pre-med student going up through leadership of departments and divisions.

Dr. Rosenow with his two grandchildren, Christian and Kate, and favorite dog Jackson.

My two grandchildren are awesome and mean the world to me. Christian was MVP for the Minnesota State High School Baseball All Stars and Kate has twice won the doubles in the Minnesota State High School Tennis Championships.

I thank the College for all it has given me!

CLASSIFIEDS

Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

MOUNT NITTANY HEALTH

Mount Nittany Health Pulmonologist Opportunity

Position Highlights include:
Mount Nittany Physician Group currently provides a range of pulmonary medicine services including interventional procedures, allergy/immunology, and sleep medicine.

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* Fully integrated EMR, electronic documentation and order entry
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Mount Nittany Medical Center, located in State College, PA, is a not-for-profit, 260 bed, acute care facility housing both inpatient and outpatient medical/surgical services. It is a growing and thriving facility offering unparalleled patient-focused care made all the more distinctive by excellent physicians, ease of access and facilities and systems engineered for the best in patient care.

State College, home to **Penn State University**, is a vibrant college town. It offers a diverse culture, a beautiful environment, excellent public and private schools, countless options for dining, theatre, sports and recreation, nightlife and more. This is all located within a safe, friendly community that makes the area perfect for raising a family. University Park Airport is located only five miles from town and State College offers easy access to Interstates 80 and 99.

Shelly Palumbo
Physician Recruiter
State College, PA
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Interested applicants may submit CV to Julia Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauver@cmhc.org . Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

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PULMONARY CRITICAL CARE POSITION

SUNY Upstate Medical University, Division of Pulmonary, Critical Care and Sleep Medicine in Syracuse, NY invites applications for a clinical faculty position at the Assistant Professor/Associate Professor level. Candidates should have strong clinical and teaching qualifications.

Sleep Medicine and Interventional Pulmonology BE/BC physicians are encouraged to apply. Responsibilities include direct patient care in the MICU, pulmonary consult service and the outpatient clinic as well as Sleep Medicine and Interventional opportunities. Supervision and teaching of medical students, residents and fellows and participation in departmental activities are required. The beautiful Central New York Fingerlakes region offers excellent schools, affordable housing and numerous recreational and social activities. MD or foreign equivalent, NYS license or eligible, BC/BE in Pulmonary and Critical Care. Interested applicants should apply to: **tuttled@upstate.edu**

SUNY Upstate Medical University is an AA/EEO/ADA employer committed to excellence through diversity. Applications from women and minorities are strongly encouraged.

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Cardiac Intensivist

OPPORTUNITY IN SOUTH FLORIDA

Memorial Healthcare System is seeking critical care physicians, dedicated to night shifts, to join the critical care team. Successful candidates will demonstrate excellent clinical skills, a broad knowledge base in critical care and dedication to providing high-quality, evidence-based care. Applicants must be BC/BE in critical care medicine. Previous experience in managing cardiac surgery patients is a plus but not a requirement. Physician(s) would have exposure to all aspects of the care of cardiac surgery patients, including mechanical devices, advanced heart failure patients, ECMO and transplant.

- 12-hour in-house shifts (7pm-7am)
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- Approximately 15 shifts per month (more if desired)
- Highly-competitive salary differential for the nocturnist position

These are full-time employed positions within the multi-specialty Memorial Physician Group. The positions offer competitive benefits and a compensation package that is commensurate with training and experience. Professional malpractice and medical liability are covered under sovereign immunity.

Memorial Healthcare System

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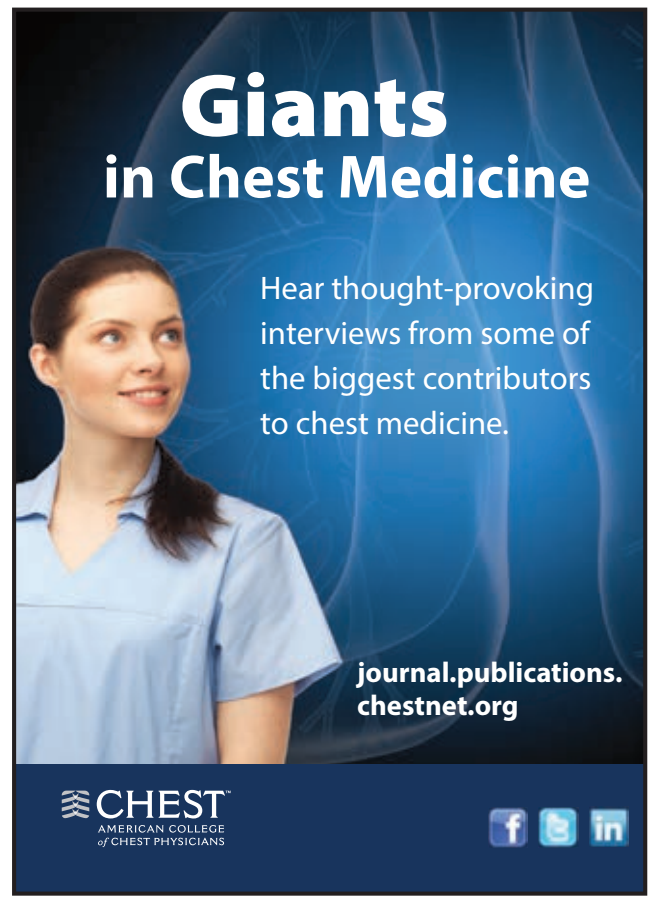

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CLASSIFIEDS

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Lauren Morgan
Tel: (267) 980-6087
lmorgan@americanmedicalcomm.com

NETWORKS Bronchiectasis, ethnic disparities, NIV for ARF, and gene expression profiling

Airway Disorders

What is the standard of care for non-CF bronchiectasis?

Bronchiectasis is a widely recognized complication of pneumonia, humoral immunodeficiency, ciliary dyskinesia syndrome, and allergic bronchopulmonary aspergillosis (ABPA). Main and colleagues have recently pointed out that the use of airway clearance techniques in bronchiectasis is physiologically quite rational and effective despite the lack of a robust supportive evidence base (Main et al. *Semin Respir Crit Care Med*. 2015;36[2]:251). In the same issue, Tay and colleagues discuss how the extrapolation of inhaled antibiotics to non-CF bronchiectasis may not be appropriate when few clinical trials have been conducted in this population. Aksamit and colleagues (Aksamit et al. *Respir Med*. 2014;108[3]:417) have used the literature to answer important questions about non-tuberculous mycobacteria (NTM) infection, a complication of approximately one-third of bronchiectasis cases. Symptomatic patients are usually treated with rifampin, ethambutol, and a macrolide thrice weekly for 12 to 18 months.


DR. GIFFORD

The extent to which lessons from clinical trials have influenced bronchiectasis care has not yet been assessed. The EMBRACE randomized, double-blind, placebo-controlled trial (Wong et al. *Lancet*. 2012;380[9842]:660) showed that azithromycin 500 mg taken thrice weekly significantly reduced the rate of infective exacerbations over a 6-month period. The BAT trial (Altenburg et al. *J Am Med Assoc*. 2013;309[12]:1251) subsequently demonstrated that azithromycin 250 mg taken daily reduced the rate of infective exacerbations and stabilized lung function after 1 year of treatment. Compared with nebulized normal saline, nebulized 7% saline improved lung function and St. George Respiratory Questionnaire domain scores in a small crossover study (Kellett et al. *Respir Med*. 2011;105[12]:1831).

Presently, we do not know whether macrolide-resistant organisms are becoming more prevalent in patients who receive these drugs for long periods of time. What constitutes best practice around surveillance for these and other airway pathogens also needs to be defined. The QOL-B inventory has been validated as a means of assessing health-related quality of life in this population (Quittner et al. *Thorax*. 2015;70[1]:12). Whether clinicians have started to use instruments like the QOL-B in daily practice is, however, unclear. The CHEST Airway Disorders Steering Committee hopes to clarify through a practice pattern survey some of these uncertainties.

Alex Gifford, MD
Steering Committee Member

Clinical Research

Ethnic disparities in clinical research: tackling a major issue in respiratory disease

Clinical research includes patient populations that fit specific criteria and subjects who are able to complete protocols requirements. The inclusion of different ethnicity, socioeconomic, and age groups has been historically underrepresented. In 1993, Congress mandated the National Institutes of Health (NIH) to include more minorities in federally funded studies to address the issue of underrepresentation.

Burchard and colleagues recently reported on the representation of minorities in published research (Burchard et al. *Am J Respir Crit Care Med*. 2015;191[5]:514). Between the years of 1993 and 2013, the inclusion of minorities in NIH-funded studies in lung disease increased slightly from 2% to 5%. The numbers were lower for nonfederally funded research. During this time, US census data revealed that people who identified themselves as belonging to a racial or ethnic minority group increased from 26.5% to 38.9%. In studies where minorities made up >25% of the participants, only 8.8% of NIH- funded studies met this criteria, making it hard to draw meaningful conclusions about these populations.

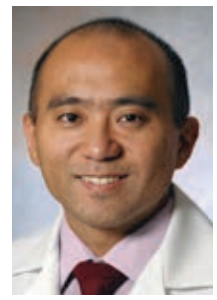
Health disparities among minorities are prominent in lung disease. There is a documented increase in the prevalence of lung disease, such as asthma, COPD, and lung cancer with higher rates of observed mortality. The authors suggested that factors contributing to underrepresentation include specific training on inclusion in clinical studies, lack of incentives to include minorities, few academic minority scientists, and lack of partnerships between minority communities and researchers. Short- and long-term strategies, such as increasing incentives to include minorities, supporting minority scientists, and working together to value research in minority populations, will improve clinical research for all.

Rebecca Persinger, MD, FCCP
Steering Committee Chair

Critical Care

High-flow oxygen in acute respiratory failure

The use of noninvasive ventilation (NIV) for acute respiratory failure (ARF) can prevent the complications of invasive mechanical ventilation. Evidence supports this approach in COPD exacerbation, cardiogenic pulmonary edema, prevention of ventilatory fatigue in the postextubation period in hypercapnic respiratory failure, immunocompromised patients with pneumonia, and postoperative ARF (Nava et al. *Lancet*. 2009;374[9685]:250). NIV improves alveolar recruitment and oxygenation, decreases the work of breathing, and affects hemodynamics. The benefit of NIV in nonhypercapnic ARF secondary to pneumonia or ARDS is less clear. A recent study compared NIV, high-flow oxygen through nasal cannula (HFNC), and standard oxygen in nonhypercapnic ARF (Frat et al. *N Engl J Med*. 2015;372[23]:2185). Most of the enrolled patients had pneumonia (64%) or extrapulmonary sepsis as cause of ARF, a $Paco_2$:Fio_2 ≤200 mm Hg (77%), and bilateral infiltrates (79%). The NIV-pressure support was tailored to a tidal volume of 7 to 10 mL/kg of predicted body weight. There was no difference in the intubation rate among the groups, but HFNC provided higher ventilator-fee days at day 28 and lowered 90-day mortality. The Pao_2:Fio_2 was higher in the NIV group; there was no difference in $Paco_2$ and respiratory discomfort and dyspnea score improved with HFNC. HFNC emerges as a reasonable option in appropriate patients with nonhypercapnic ARF. Possible reasons for its benefit are lower tidal volumes provided by the lack of pressure support in the non-NIV patients, better patient comfort that could impact mortality-associated variables like ICU-delirium, or better secretion clearance with heated humidification through a nasal interface.


DR. KAKAZU

Maximiliano A. Tamae Kakazu, MD
Steering Committee Member

Interstitial and Diffuse Lung Disease

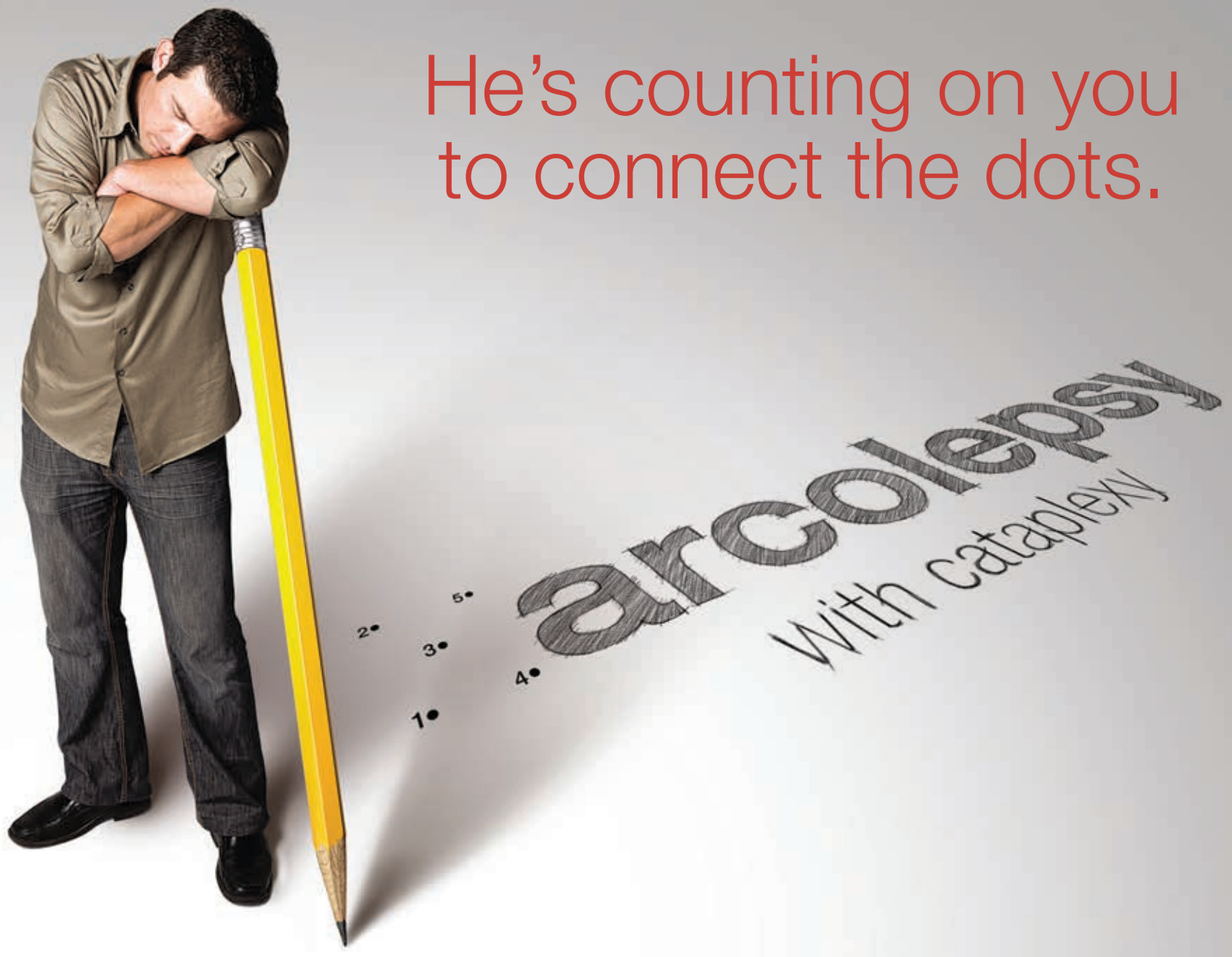
Gene expression profiling

Gene expression profiling studies have demonstrated that transcriptional changes are present in the lung of idiopathic pulmonary fibrosis (IPF) subjects. Gene expression changes are dramatic and involve large numbers of genes on the order of a few thousand differentially expressed genes. In summary, these studies have consistently identified similar genes and pathways that are also expressed directly in fibrotic lung such as genes associated with formation, degradation, encoding immunoglobulins, complement, and chemokines. A significant change in IPF lungs is the abnormal expression of developmental pathways. However, specific studies have identified successfully transcriptional profiles associated with rapid disease progression and acute exacerbations in IPF. More recently, two molecular subtypes of IPF have been identified based on a strong gene expression signature, containing a number of genes that have previously been shown to be upregulated in IPF, particularly dysregulated cilia genes.


DR. CARBONE

In fact, cilium gene abnormalities have been confirmed in multiple lung specimens from the same subjects and in an independent cohort of subjects with IPF. In addition to being associated with greater expression of MUC5B and matrix metalloproteinase, greater cilium gene expression is associated with microscopic honeycombing but not fibroblastic foci. Notably, the work published online (Kim et al. *Lancet*. 2015;[3]:475) shows that identifying a genomic signature that predicts usual interstitial pneumonia is feasible and could be the first step for a molecular test avoiding invasive investigations in IPF diagnosis (Maher et al. *Lancet*. 2015;3[6]:423).

Roberto G. Carbone, MD, FCCP
Steering Committee Member



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1. Sturzenegger C, Bassetti CL. The clinical spectrum of narcolepsy with cataplexy: a reappraisal. *J Sleep Res.* 2004;13(4):395-406.
2. Bassetti CL. Spectrum of narcolepsy. In: Baumann CR, Bassetti CL, Scammell TE, eds. *Narcolepsy: Pathophysiology, Diagnosis, and Treatment.* New York, NY: Springer Science+Business Media; 2011:309-319.

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