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Albuterol costs soared after CFC inhaler ban

BY AMY KARON
Frontline Medical News

Privately insured patients with asthma faced an 81% rise in out-of-pocket costs for albuterol and used slightly less of the medication after the Food and Drug Administration banned chlorofluorocarbon-based inhalers, researchers reported in an article that was published online in JAMA Internal Medicine.

But the ban did not appear to affect either the rates of hospitalization or those of emergency department or outpatient visits for asthma, said Dr. Anupam Jena of Massachusetts General Hospital in Boston and his associates.

"The impact of the FDA policy on individuals without insurance who faced greater increases in out-of-pocket costs warrants further exploration," the researchers recommended.

Concerns about ozone depletion led the FDA in 2005 to announce a ban on CFC inhalers that became effective at the end of 2008.

As the result of that decision, patients were left with pricier branded hydrofluoroalkane albuterol inhalers, Dr. Jena and his associates noted (JAMA Intern. Med. 2015 May 11 [doi:10.1001/jamainternmed.2015.1665]).

To investigate the economic and clinical effects of this

See **Albuterol** • *page 8*

Look for insulin insufficiency in cystic fibrosis

Linked to poor lung function, death.

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – Cystic fibrosis–related diabetes is a unique disease, and it requires a different mindset on the part of the treating physician.

"The risk of cardiovascular death drives a lot of the recommendations for management of our patients with type 1 and type 2 diabetes, but this doesn't apply in cystic fibrosis. Patients with cystic fibrosis–related diabetes do not appear to get macrovascular complications. These patients have other, more important concerns – namely, survival. They die from their CF lung disease. Diabetes is important, but we have to remember that in CF, lung function and nutrition come first. It's our job to work around that," Dr. Antoinette Moran said at the Pediatric Academic Societies annual meeting.

Diabetes is the most common comorbidity associated with CF. And it spells big trouble. It's associated with pancreatic insufficiency, liver dysfunction, requirement for corticosteroids, and prognostically with undernutrition, worse pulmonary function, and early death, noted Dr. Moran, professor

See **CF** • *page 12*

INSIDE

Program curbed excess prescribing of antibiotics in the NICU

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – Neonatal intensive care unit (NICU) care in the past had been frought with protocol-driven use of antibiotics without a consistent plan for cessation, but a well-executed antibiotic stewardship strategy can safely reduce unnecessary prescribing – as demonstrated at the 90-bed, level-IIIC NICU at Parkland Memorial Hospital, Dallas.

Results of the Surveillance and Correction of Unnecessary Antibiotic Therapy (SCOUT) study showed that total antibiotic days of therapy (DOT) in the Parkland NICU dropped by 27% following implementation of an antibiotic stewardship

See **NICU** • *page 9*

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

HELP HER WRITE FUTURE CHAPTERS

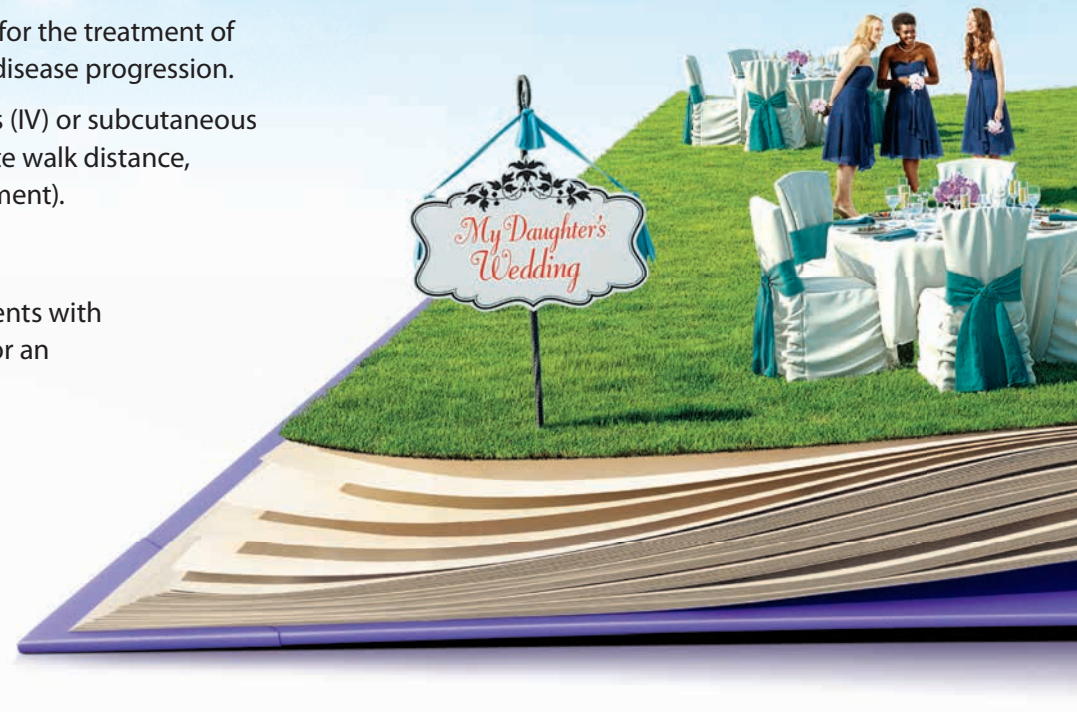
OPSUMIT® (macitentan) is the only ERA approved to delay disease progression as both monotherapy and in combination with PDE-5 inhibitors or inhaled prostanoids[1]

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.

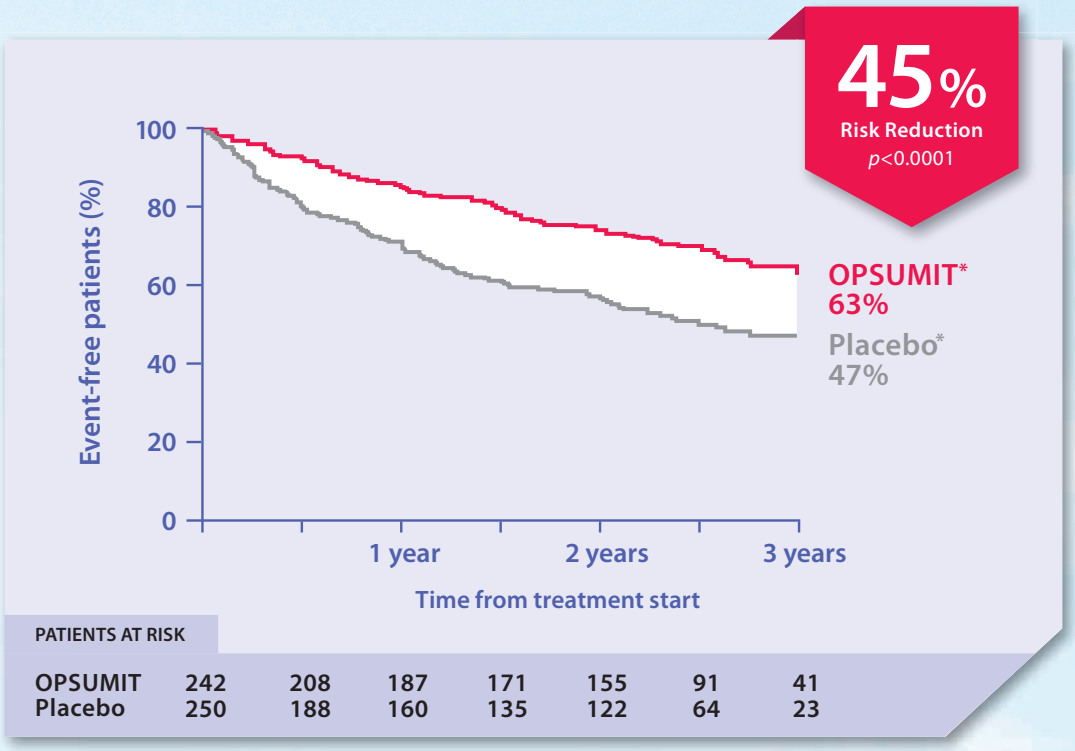
FUTURE. FORWARD. Opsumit® macitentan tablets 10 mg

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.

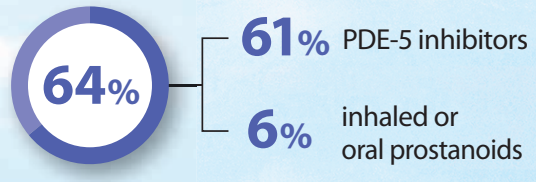
Keep disease progression in mind from the start of therapy: OPSUMIT is the only ERA approved to delay disease progression in FC II and III patients[1]

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.

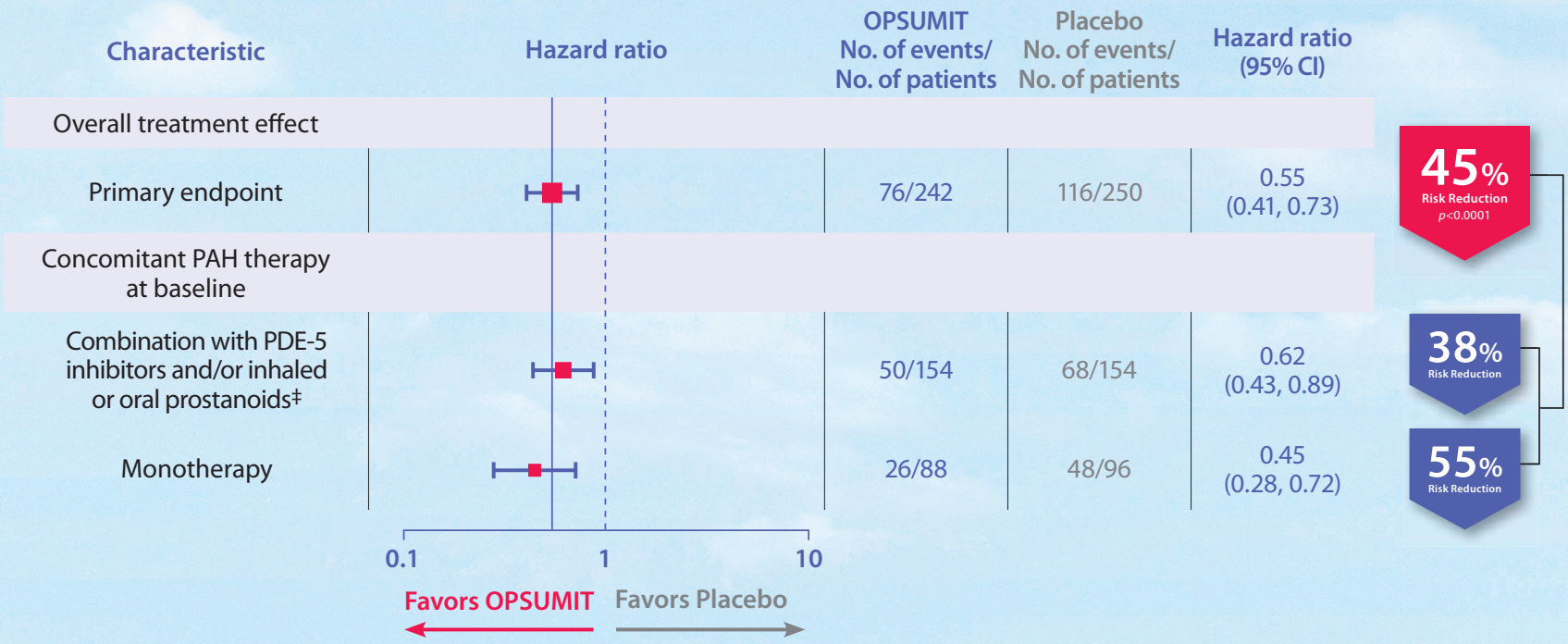
Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

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

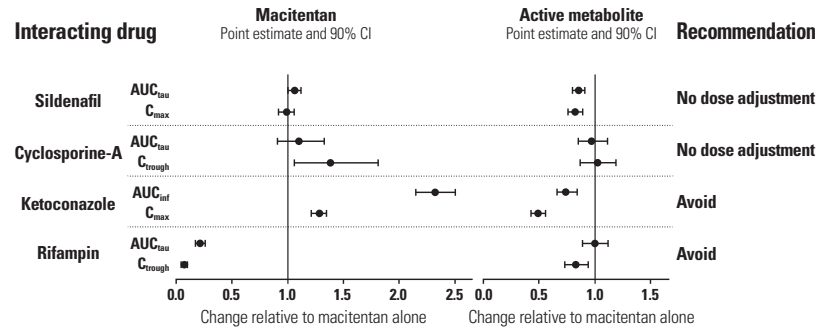
In vitro studies

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

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. February 2015.

Inhaler costs soared

Albuterol *from page 1*

shift, the researchers analyzed private insurance data during the span from 2004 to 2010 on 109,428 adults and 37,281 children with asthma.

The average out-of-pocket cost of an albuterol prescription rose from $13.60 (95% confidence interval, $13.40-$13.70) in 2004 to $25.00 (95% CI, $24.80-$25.20) in 2008, just after the ban went into effect, the researchers reported.

By 2010, the average cost of a prescription had dropped to $21.00 (95% CI, $20.80-$21.20).

"Steep declines in use of generic CFC inhalers occurred after the fourth quarter of 2006 and were almost fully offset by increases in use of hydrofluoroalkane inhalers," the researchers reported.

Furthermore, every $10 increase in out-of-pocket albuterol prescription costs was tied to about a 0.92 percentage point decline in patients' use of the inhalers (95% CI, −1.39 to −0.44; $P < .001$) in adults, and a 0.54 percentage point in children (95% CI, −0.84 to −0.24; $P = .001$), according to Dr. Jena and his associates .

Usage did not vary significantly between adults and children or among patients who had persistent or nonpersistent asthma, the researchers added.

VITALS

Key clinical point: The FDA ban on chlorofluorocarbon-based albuterol inhalers sharply increased out-of-pocket costs and slightly decreased inhaler usage.

Major finding: Average out-of-pocket cost of albuterol inhalers rose by 50% after the ban was passed.

Data source: Analysis of private insurance data from 109,428 adults and 37,281 children with asthma from 2004 through 2010.

Disclosures: The National Institutes of Health, National Institute on Aging, and University of Minnesota funded the study. The investigators declared no relevant conflicts of interest.

IN THIS ISSUE

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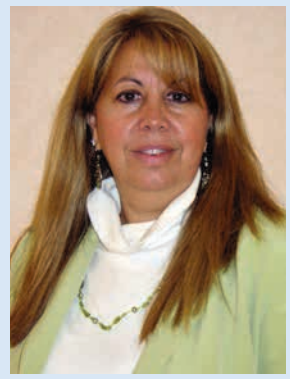

Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of *CHEST* Physician.

VIEW ON THE NEWS

Delaying the CFC ban would have balanced interests of patients, society

The 2008 FDA ban on albuterol inhalers containing chlorofluorocarbons was questioned at the time because the CFCs emitted from inhalers have an insignificant effect on ozone and because of the anticipated costs of transitioning to hydrofluoroalkane inhalers for patients with respiratory disease.

Whether banning chlorofluorocarbon inhalers will lead to any improvement in the environment is unclear. It is clear that the ban has increased health care costs and improved the bottom line of pharmaceutical companies that are making hydrofluoroalkane-based inhalers.

Although albuterol inhalers have been in use for more than 30 years, pharmaceutical companies have used the chlorofluorocarbon ban as an opportunity to raise the price on inhalers from approximately $13 for a generic formulation to more than $50 today.

In this unique situation, it would have made more sense to not ban chlorofluorocarbon inhalers until hydrofluoroalkane inhalers were available in generic formulations. This would have balanced the best interests of society and the best interests of individuals with respiratory disease, allowing the FDA to protect the environment without making inhalers expensive and unaffordable for many.

Dr. Joseph Ross is at the Yale University School of Medicine in New Haven, Conn., and disclosed FDA research funding related to medical device surveillance and clinical trial data sharing. Dr. Rita Redberg is at the University of California, San Francisco, and made no relevant disclosures. Their comments are based on their accompanying editorial (JAMA Intern. Med. 2015 May 11 [doi:10.1001/jamainternmed.2015.1696]).

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Program cut excess prescribing

NICU *from page 1*

program featuring hard stops built into the electronic medical record, Dr. Joseph B. Cantey reported at the annual meeting of the Pediatric Academic Societies.

This overall reduction in antibiotic utilization was accomplished through improvements in the three specific categories of NICU antibiotic use targeted for intervention in the SCOUT study: treatment courses of more than 48 hours for "rule-out sepsis" and treatment lasting longer than 5 days for pneumonia or "culture-negative sepsis."

The proportion of antibiotic treatment courses for rule-out sepsis that were discontinued by 48 hours when cultures were sterile tripled from 32% to 95% between a 9-month baseline period and a second 9-month period after implementation of the antibiotic stewardship program. The proportion of courses of antibiotics for pneumonia that were limited to 5 days doubled from 36% to 72%. Similarly, there was a doubling in the proportion of treatment courses for "culture-negative sepsis" limited to 5 days, with the rate going from 31% to 62%, said Dr. Cantey, a pediatrics fellow in training at the University of Texas Southwestern Medical Center, Dallas.

During the 9-month baseline surveillance period, in which there were 1,607 patients in the NICU, the total antibiotic use was 343 DOT per 1,000 patient-days.

During period two with the intervention in place, there were 895 NICU patients, and 251 DOT per 1,000 patient-days.

The DOT, a commonly used measure in the field of infectious diseases, is determined by multiplying the number of doses by the dosing interval. DOTs in patients on multiple antibiotics are additive, he explained.

During the baseline observation period, 94% of all antibiotic use in the NICU was empiric therapy for suspected infection. More specifically,

Continued on following page

VITALS

Key clinical point: Total antibiotic utilization in a level-IIIC neonatal intensive care unit was safely reduced by 27% through a formal antibiotic stewardship program.

Major finding: The rate of discontinuation of courses of antibiotics given for "rule-out sepsis" by 48 hours tripled from 32% at baseline to 95% post intervention.

Data source: This prospective study carried out in a 90-bed NICU involved an initial 9-month baseline observation period and a second 9-month period starting after implementation of the stewardship program.

Disclosures: The study was supported by a Gerber Novice Researcher Award from the Gerber Foundation. The presenter reported having no relevant financial disclosures.

In the SCOUT study, total antibiotic days of therapy dropped by 27% after implementing an antibiotic stewardship program built into the electronic medical record.

Continued from previous page

63% of all antibiotic use was for rule-out sepsis. And while many of the courses of antibiotics given for this reason that exceeded the 48-hour limit during the baseline period did so by only one or two doses, those extra doses added up to 41 DOT per 1,000 patient-years, making this a worthy target for intervention. Together with treatment of pneumonia or "culture-negative sepsis" for longer than 5 days, these three high-yield targets accounted for 87% of all antibiotic use in the NICU during the baseline period, Dr. Cantey said.

The infants occupying the NICU during the two 9-month study periods were virtually identical in terms of their characteristics and reasons for admission.

The proportion of antibiotic treatment courses for rule-out sepsis that were discontinued by 48 hours when cultures were negative tripled from 32% to 95%.

Antibiotics are the most commonly prescribed medications in NICUs. Their use has been associated with adverse NICU outcomes, including increased risks of necrotizing entero-

colitis, late-onset sepsis, and death in infants with birth weights below 1,500 g, as well as an increase in multidrug-resistant organisms, he noted.

In SCOUT, the composite outcome of necrotizing enterocolitis, late-onset sepsis, or death didn't differ between the two study periods: 17.1% at baseline and 15.8% during the intervention period. Similarly, the incidence of colonization with multidrug-resistant organisms was 1.4% during the baseline period and not significantly different at 1% after implementation of the antibiotic stewardship program. Larger multicenter studies with pooled data will be required to determine whether antibiotic stewardship in NICUs affects neonatal outcomes, Dr. Cantey said.

Those extra one or two doses added up to 41 DOT per 1,000 patient-years, making this a worthy target.

DR. CANTEY

He added that he and his coinvestigators are now trying to identify additional NICU scenarios in which antibiotics can safely be withheld. One likely candidate: asymptomatic preterm infants exposed to premature rupture of membranes. The investigators also hope to utilize the ongoing prospective surveillance element of Parkland's NICU antibiotic stewardship program to identify the safe minimum treatment duration for common conditions such as urinary tract infections, sepsis, and necrotizing enterocolitis.

Audience members were effusive in their praise of the SCOUT study and the Parkland program. They wanted to hear more details about how the physician behavior change was accomplished. Dr. Cantey said that the three intervention targets were approved by the NICU medical director and the plan was disseminated to all the neonatologists, nurse practitioners, fellows, and residents. It was important to be able to assure everyone that outcomes would be prospectively monitored closely to ensure safety. The toughest task, he added, was to create the hard stops in the electronic medical record so that, for example, treatment for rule-out sepsis would automatically stop at 48 hours: skilled information technologists were essential.

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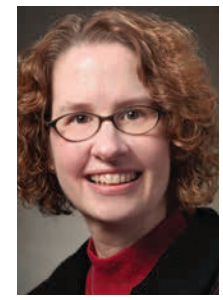
EDITOR'S COMMENT



Dr. Susan Millard, FCCP, comments: Antibiotic stewardship is becoming a necessity to decrease prolonged utilization of antibiotics. This service has been used at Helen DeVos Children's Hospital for the past few years, and I wouldn't know what to do without it now!

Panel votes 12-1 for approval of combo drug for CF

BY ELIZABETH MECHCATIE
Frontline Medical News

AT AN FDA ADVISORY COMMITTEE MEETING

GAITHERSBURG, MD. – A fixed-dose combination of ivacaftor, already approved for a cystic fibrosis indication, and lumacaftor will likely be the first drug combination treatment approved for the most common type of cystic fibrosis, based on a Food and Drug Administration advisory panel's near unanimous support for approval.

At a meeting May 12, the FDA's Pulmonary-Allergy Drugs Advisory Committee voted 12-1 that the data on the safety and efficacy of the fixed-dose combination of ivacaftor, 250 mg, and lumacaftor, 400 mg, administered twice a day, support approval for treating patients aged 12 years and older with CF who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. About half of patients with CF are F508del homozygous, and if approved, this would be the first treatment that addresses the underlying cause of CF in these patients, according to Vertex Pharmaceuticals, the manufacturer of both drugs.

FDA NEWS

Lumacaftor "facilitates the processing and trafficking of F508del-CTFR to increase its amount at the cell surface," while ivacaftor "potentiates the channel-open probability of F508del-CTFR delivered to the cell surface by" lumacaftor, according to Vertex. Ivacaftor (Kalydeco) is a CFTR potentiator approved in January 2012 for treating patients with the G551D mutation, who represent about 4% of patients with CF – its indications have been expanded since that time to include other CFTR gene mutations.

In two phase III studies, the proposed dose and another fixed-dose combination of the two drugs were compared with placebo for 24 weeks in about 1,100 patients homozygous for the F580del mutation who were aged 12 years and over. At 24 weeks, the absolute change in percent-predicted forced expiratory volume in 1 second (ppFEV1) over placebo, the primary efficacy endpoint, was a mean of 2.6% and 3.0% among those treated with the 400 mg/250 mg fixed dose every 12 hours, which were statistically significant changes. In an extension study, the effect was sustained through 48 weeks. There also were reductions in pulmonary exacerbations, improvements in body mass index, and CFQ-R (Cystic Fibrosis Questionnaire-Revised) improvements – secondary end-

Continued on following page

Insulin Insufficiency

CF *from page 1*

of pediatrics and chief of the division of pediatric endocrinology and diabetes at the University of Minnesota, Minneapolis.

The prevalence of cystic fibrosis–related diabetes (CFRD) is age related. It's rare in children, but the prevalence climbs to about 15% in adolescents, 40% in 20- to 39-year-olds, and 55% after age 40.

"In fact, more than 80% of CF patients with the most severe mutations have diabetes by the time they're 40," according to Dr. Moran, who was lead author of CFRD management guidelines released last year by the International Society for Pediatric and Adolescent Diabetes (Pediatr. Diabetes 2014 Sep;15 Suppl 20:65-76).

CFRD is not an autoimmune disease. Ketones are rare. Glycosylated hemoglobin levels are spuriously low. And the definitive treatment for CFRD is insulin.

"Remember, you're not just treating hyperglycemia, you're treating insulin deficiency. Insulin deficiency is really the hallmark of this disease. It is progressive and eventually severe, but not complete – unlike in type 1 diabetes," she observed. "Treatment of patients in their well state is similar to treating type 1 diabetes in the honeymoon phase. However, during acute illness patients become extremely insulin resistant. It's a black hole that you can pour insulin into, and sometimes you can't get them to budge. Then a couple of months later they're insulin sensitive again."

Multiple studies have demonstrated that diabetes has a negative impact upon survival in patients with CF. Both hyperglycemia and insulin insufficiency have negative impacts upon the CF lung disease.

Insulin is a potent anabolic hormone that's necessary for maintenance of body weight and lean body mass, and insulin insufficiency leads to a catabolic state which accelerates pulmonary decline in CF. Studies show that nutritional status and pulmonary function start to decline in CF patients several years before they're diagnosed with diabetes. Thus, by the time CFRD is diagnosed, patients have already experienced several years of insulin insufficiency, with adverse consequences.

Why are we calling this diabetes? These patients have repeated bouts of acute illness.

DR. MORAN

Moreover, when blood glucose levels exceed 144 mg/dL, glucose appears in the airways of CF patients. That's not good. It probably promotes pulmonary infection. Anecdotal evidence suggests hyperglycemia makes sputum thicker and more difficult to clear as well as boosting bacterial growth. And continuous glucose monitoring studies conducted in patients with CFRD indicate they spend roughly half of each day with a blood glucose in excess of 144 mg/dL.

Aggressive screening and early initiation of insulin therapy help reverse chronic weight loss and reduce mortality in patients with CFRD. The various guidelines recommend annual screening for diabetes in CF patients starting by age 10.

"I personally believe it should begin much earlier than that," Dr. Moran said, citing a study led by her Minnesota colleague Dr. Katie L. Ode that showed that abnormal glucose tolerance was already present in 41% of children with CF at ages 6-9, and that those children had a high rate of early-onset CFRD (Pediatr. Diabetes 2010 Nov;11:487-92).

The oral glucose tolerance test, performed when the patient is clinically stable, is the screening tool of choice for CFRD.

"It's not that it's such a great test – we all know it has problems – but the other tests perform poorly in CF. And a diagnosis based upon an oral glucose tolerance test correlates with prognosis and future outcomes, so you get meaningful data when you do it," she explained.

Evidence-based guidelines for CFRD put forth jointly by the American Diabetes Association, Cystic Fibrosis Foundation, and Lawson Wilkins Pediatric Endocrinology Society (Diabetes Care 2010;33:2697-2708) emphasize that, unlike in patients without CF, the diagnosis of CFRD can be made while a patient is hospitalized with an acute illness. The criterion is fasting or postprandial hyperglycemia persisting for more than 48 hours after hospitalization.

"Why are we calling this diabetes? These patients have repeated bouts of acute illness. The CF patient you're seeing today in the hospital may very well be back in 5 months, and again 2 months after that. It's a frequent event in these patients, and when their diabetes persists for longer than 48 hours it tends to persist for weeks before their need for insulin goes away until the next time they get sick. But most of these patients spend a substantial amount of time each year hyperglycemic. And most importantly, if you use as your date of diagnosis diabetes that's present at the time of an acute illness, it correlates with microvascular complications and with mortality. So it establishes a meaningful start point for future risk," Dr. Moran said.

She reported financial relationships with Novo Nordisk and Vertex.

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EDITOR'S COMMENT

Dr. Vera A. De Palo, MBA, FCCP, comments: Cystic fibrosis-related diabetes (CFRD), a very common co-morbidity in cystic fibrosis (CF), is different from the diabetes mellitus that clinicians are most familiar with and requires a mindset and approach that is unique. Dr. Moran explains that the prevalence is age-related and by the time that CFRD is diagnosed, several years of insulin insufficiency with adverse consequences have occurred. Both the hyperglycemia and insulin insufficiency can accelerate the pulmonary decline and have a negative impact on survival. Earlier recognition of CFRD and initiation of treatment according to the evidence-based guidelines are important in caring for patients with CF.

Insulin at diagnosis, new agent are 'game changers'

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – Promising developments in the treatment and perhaps even prevention of cystic fibrosis–related diabetes are on the horizon – and they're coming none too soon.

This is a field in need of a kick start, Dr. Antoinette Moran said at the annual meeting of the Pediatric Academic Societies.

She cited her recent review of 664 cystic fibrosis patients treated at the University of Minnesota during 2008-2012.

Overall mortality in those with cystic fibrosis–related diabetes (CFRD) was unchanged from the high rates seen in a similar review covering 2003-2008, despite adoption of an institutional policy of aggressive screening for diabetes and early initiation of insulin therapy upon diagnosis of CFRD (Am. J. Respir. Crit. Care Med. 2015;191:194-200).

"Certainly screening and early institution of insulin are critical, but we seem to have come up against a wall. Honestly, at the University of Minnesota there is no way that we can be more aggressive than we already are with screening and with insulin. We have done as much as we can. So we need to think of something different to move this to the next stage," said Dr. Moran, professor of pediatrics and chief of the division of pediatric endocrinology and diabetes at the University of Minnesota, Minneapolis.

She highlighted what she considers two of the most promising novel areas of CFRD research. One involves high-priority studies laying the groundwork for possible initiation of insulin therapy in cystic fibrosis (CF) patients even before they are diagnosed with CFRD, possibly starting in infancy.

The other major event is the anticipated Food and Drug Administration approval of a fixed-dose combination of ivacaftor and lumacaftor, a combined potentiator and corrector of the CF transmembrane conductance regulator (CFTR). Mutations in this chloride conduction channel are the most common cause of CF.

Marketing approval for the new combination agent, which has breakthrough drug designation, is believed to be imminent.

"This is absolutely fascinating and a real game changer in the world of CF: the ability to fix CFTR, the abnormal CF chloride channel," Dr. Moran said. "It's expected that virtually every CF patient in the country is going to be on these drugs once the combination is approved."

A large multicenter postmarketing study known as PROSPECT is in place and ready to start once the ivacaftor/lumacaftor combination receives approval.

PROSPECT will capture patients right before they start the agent and then follow them longitudinally. Dr. Moran is principal investigator for the GIFT (Gastrointestinal/Glucose and Insulin Functional Testing) substudy of PROSPECT. This 75-patient study will entail oral glucose tolerance testing with insulin, glucose, and C-peptide levels obtained at baseline and 1, 6, and 12 months.

The rationale for GIFT comes from the fact that CFTR mutations are present in the pancreatic beta cells of CF patients.

An earlier five-patient pilot study conducted by Dr. Moran suggested ivacaftor might improve insulin secretion in patients with CF. This observation raises the question: "If we could start the drugs in very young children, might it prevent the development of diabetes? If the basic CFTR defect impacts beta cell function, it suggests this is going to be the way to get around that impasse – that treatment other than insulin will prevent or at least partially treat CFRD," she said.

Another approach to preventing CFRD is being pursued by Dr. Moran's colleague, Dr. Katie Larson Ode, a pediatric diabetologist at the University of Iowa, Iowa City. She showed that abnormal glucose tolerance was already present in 41% of 6- to 9-year-olds with CF, and among that subgroup, 42% developed early-onset CFRD at an average age of 11 years in girls and 12 years in boys, in contrast to the general Minnesota CF population, where the average age of onset of CFRD is age 23 years.

Moreover, the 59% of 6- to 9-year-olds with normal glucose tolerance had impaired insulin secretion. Their insulin secretion on oral glucose tolerance testing was half that of control children without CF.

This raises a question: Were these CF children born with these defects, or do the abnormalities evolve slowly during childhood?

Dr. Ode is attempting to find out by performing annual oral glucose tolerance tests starting in infancy at the time of CF diagnosis. She is looking prospectively at the relationships between glucose and insulin levels and exocrine function, growth, inflammation, and pulmonary function, with the subjects' unaffected siblings serving as controls.

"If those infants and toddlers with CF have abnormal insulin secretion and if it correlates with worse clinical parameters, we're really going to have to consider whether we should be starting insulin right away in these babies. After all, we don't wait to start vitamin D in CF infants until they develop rickets. We treat everything else preventively – we may need to think about doing that with insulin," said Dr. Moran.

In her 664-patient review of the University of Minnesota experience with CF during 2008-2012, overall mortality in those with CFRD was 1.8 per 100 person-years ,compared with 0.5 per 100 person-years in CF patients without diabetes.

In patients with mild CF genotypes, the risk of mortality was 20% in those with CFRD compared with 2% without diabetes.

In patients with severe genotypes, overall mortality was 12% in those with CFRD, threefold higher than in those without diabetes.

Dr. Moran reported having financial relationships with Novo Nordisk and Vertex, which is developing ivacaftor/lumacaftor.

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Continued from previous page

points that favored the treatment arms, according to the company.

The most common adverse events were typical for patients with CF and similar between the treatment groups.

There was an imbalance in respiratory adverse events affecting those on the drug combination (23% vs. almost 14% among those on placebo), but most occurred early in treatment, were generally mild to moderate, and resolved without stopping treatment. Those on the drug combination also had more liver-related serious adverse events (three cases among those on the proposed dose and none among those on placebo).

At the time the phase III studies were being planned, the FDA and the company agreed that an ivacaftor monotherapy arm was not needed and that demonstration of the combination's superiority over placebo would be adequate to show efficacy. In the phase III studies, however, the combination effect was smaller than expected, and there was no substantial evidence indicating that the efficacy of the combination was greater than that of ivacaftor alone, an issue raised by the FDA reviewers.

About half of patients with CF are F508del homozygous. If approved, this drug would be the first treatment that addresses the underlying cause of CF.

Despite the lack of monotherapy arms and the inability to determine the contribution of the individual components to the treatment effects, the panel agreed that the drug combination had been shown to be efficacious and voted 13-0 that the data supported the safety of treatment.

Panelists commented that the risks appeared to be minimal and that patients could be monitored for liver function test abnormalities and respiratory function, which were manageable.F

Voting in favor of approval, pediatric pulmonologist Dr. Robert Castile, professor of pediatrics at Ohio State University, Columbus, said he was particularly impressed with the lack of decline in FEV1 over 48 weeks among those treated with the combination "and probably more impressed over the steady increase in BMI over the same period." He added that he balanced those benefits with what he considered minimal risks with the drug with appropriate monitoring.

If the FDA grants approval, Vertex plans to market the combination product as Orkambi. The FDA usually follows the recommendations of its advisory panels. Panelists were cleared of conflicts before the meeting.

About 30,000 people in the United States have cystic fibrosis, about half of whom are homozygous for the F508del, the most common CF mutation, according to the FDA.

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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.

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*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®

Lulling you to sleep… with ICD-10 sleep codes

BY DR. MICHAEL E. NELSON, FCCP

As we continue our adventure into ICD-10 with the sleep codes, one will notice a couple of new instructions, "code first" and "code with." The "code first" direction will be found with codes where the diagnosis is a manifestation of another disease. For example, with *G47.42 Narcolepsy in conditions classified elsewhere*, one sees the "code first" direction. If the narcolepsy was a result of an intracranial injury, then the correct coding sequence would be a code from the S06 family (eg, *S06.0X1 Concussion with loss of consciousness of 30 minutes or less*) followed by either *G47.421* or *G47.472*, dependent upon the presence or absence of cataplexy.

According to the **ICD-10-CM Official Guidelines for Coding and Reporting** available at www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html, the "code also" note instructs that two codes may be required to fully describe a condition, but this note does not provide sequencing direction. The ICD-10 CM codes for common sleep diagnoses are listed below. Please note that the *G25.81 restless legs syndrome* diagnosis is not found in "Sleep disorders" code set but rather in the G25 "Other extrapyramidal and movement disorders" set.

Sweet dreams!

G47 Sleep disorders		
Excludes 2: nightmares (F51.5) nonorganic sleep disorders (F51.-) sleep terrors (F51.4) sleepwalking (F51.3)		
G47.0	**Insomnia**	
	Excludes 2: alcohol related insomnia (F10.182, F10.282, F10.982) drug-related insomnia (F11.182, F11.282, F11.982, F13.182, F13.282, F13.982, F14.182,F14.282, F14.982, F15.182, F15.282, F15.982, F19.182, F19.282, F19.982) idiopathic insomnia (F51.01) insomnia due to a mental disorder (F51.05) insomnia not due to a substance or known physiological condition (F51.0-) nonorganic insomnia (F51.0-) primary insomnia (F51.01) sleep apnea (G47.3-)	
	G47.00	**Insomnia, unspecified** Insomnia NOS
	G47.01	**Insomnia due to medical condition** Code also associated medical condition
	G47.09	**Other insomnia**
G47.1	**Hypersomnia**	
	Excludes 2: alcohol-related hypersomnia (F10.182, F10.282, F10.982) drug-related hypersomnia (F11.182, F11.282, F11.982, F13.182, F13.282, F13.982, F14.182,F14.282, F14.982, F15.182, F15.282, F15.982, F19.182, F19.282, F19.982) hypersomnia due to a mental disorder (F51.13) hypersomnia not due to a substance or known physiological condition (F51.1-) primary hypersomnia (F51.11) sleep apnea (G47.3-)	
	G47.10	**Hypersomnia, unspecified** Hypersomnia NOS
	G47.11	**Idiopathic hypersomnia with long sleep time** Idiopathic hypersomnia NOS
	G47.12	**Idiopathic hypersomnia without long sleep time**
	G47.13	**Recurrent hypersomnia** Kleine-Levin syndrome Menstrual related hypersomnia
	G47.14	**Hypersomnia due to a medical condition** Code also associated medical condition
	G47.19	**Other hypersomnia**
G47.2	**Circadian rhythm sleep disorders** Disorders of the sleep wake schedule Inversion of nyctohemeral rhythm Inversion of sleep rhythm	
	G47.20	**Circadian rhythm sleep disorder, unspecified type** Sleep wake schedule disorder NOS
	G47.21	**Circadian rhythm sleep disorder, delayed sleep phase type** Delayed sleep phase syndrome
	G47.22	**Circadian rhythm sleep disorder, advanced sleep phase type**
	G47.23	**Circadian rhythm sleep disorder, irregular sleep wake type** Irregular sleep-wake pattern
	G47.24	**Circadian rhythm sleep disorder, free running type**
	G47.25	**Circadian rhythm sleep disorder, jet lag type**
	G47.26	**Circadian rhythm sleep disorder, shift work type**
	G47.27	**Circadian rhythm sleep disorder in conditions classified elsewhere** Code first underlying condition
	G47.29	**Other circadian rhythm sleep disorder**
G47.3	**Sleep apnea**	
	Code also any associated underlying condition **Excludes 1:** apnea NOS (R06.81) Cheyne-Stokes breathing (R06.3) pickwickian syndrome (E66.2) sleep apnea of newborn (P28.3)	
	G47.30	**Sleep apnea, unspecified** Sleep apnea NOS
	G47.31	**Primary central sleep apnea**
	G47.32	**High altitude periodic breathing**
	G47.33	**Obstructive sleep apnea (adult) (pediatric)** Excludes 1: obstructive sleep apnea of newborn (P28.3)
	G47.34	**Idiopathic sleep related nonobstructive alveolar hypoventilation** Sleep related hypoxia
	G47.35	**Congenital central alveolar hypoventilation syndrome**
	G47.36	**Sleep related hypoventilation in conditions classified elsewhere** Sleep related hypoxemia in conditions classified elsewhere Code first underlying condition
	G47.37	**Central sleep apnea in conditions classified elsewhere** Code first underlying condition
	G47.39	**Other sleep apnea**
G47.4	**Narcolepsy and cataplexy**	
	G47.41	**Narcolepsy**
		G47.411 **Narcolepsy with cataplexy**
		G47.419 **Narcolepsy without cataplexy** Narcolepsy NOS
	G47.42	**Narcolepsy in conditions classified elsewhere** Code first underlying condition
		G47.421 **Narcolepsy in conditions classified elsewhere with cataplexy**
		G47.429 **Narcolepsy in conditions classified elsewhere without cataplexy**
G47.5	**Parasomnias** **Excludes 1:** alcohol induced parasomnia (F10.182, F10.282, F10.982) drug induced parasomnia (F11.182, F11.282, F11.982, F13.182, F13.282, F13.982, F14.182,F14.282, F14.982, F15.182, F15.282, F15.982, F19.182, F19.282, F19.982) parasomnia not due to a substance or known physiological condition (F51.8)	
	G47.50	**Parasomnia, unspecified** Parasomnia NOS
	G47.51	**Confusional arousals**
	G47.52	**REM sleep behavior disorder**
	G47.53	**Recurrent isolated sleep paralysis**
	G47.54	**Parasomnia in conditions classified elsewhere** Code first underlying condition
	G47.59	**Other parasomnia**
G47.6	**Sleep related movement disorders** **Excludes 2:** restless legs syndrome (G25.81)	
	G47.61	**Periodic limb movement disorder** Periodic limb movement disorder
	G47.62	**Sleep related leg cramps**
	G47.63	**Sleep related bruxism** psychogenic bruxism (F45.8)
	G47.69	**Other sleep related movement disorders**
G47.8	**Other sleep disorders**	
G47.9	**Sleep disorder, unspecified** Sleep disorder NOS	

Strong association between OSA, depression

BY SHARON WORCESTER
Frontline Medical News

DENVER – Men with previously undiagnosed severe obstructive sleep apnea and excessive daytime sleepiness have a more than four-fold increase in the risk of depression, compared with those without either condition, according to findings from a population-based cohort study.

Those with both severe obstructive sleep apnea (OSA) and excessive daytime sleepiness (EDS) also have a 3.5 times greater risk of depression than do those with either OSA or EDS alone, Carol Lang, Ph.D., reported during a press briefing at an international conference of the American Thoracic Society.

The findings have important implications for clinicians treating patients with depression; clinicians should recognize the risk of OSA in men with depression, and should screen those presenting with OSA – regardless of whether sleepiness is present, said Dr. Lang of the University of Adelaide, Australia.

Study subjects were 1,875 community dwelling Australian men aged 35-83 years who were assessed for depression using the Beck Depression Inventory/Centre for Epidemiological Studies Depression Scale (CES-D) at two times points about 5 years apart. A random sample of 857 men without previously diagnosed OSA underwent at-home polysomnography and completed the Epworth Sleepiness Scale questionnaire, and 1,660 men without depression at baseline were included in the analysis of incident depression.

Previously undiagnosed mild-to-moderate and severe OSA were associated with depression prevalence (adjusted odds ratio 2.1), and this was true even after adjusting for confounders and EDS.

EDS also was associated with depression (adjusted OR, 1.1). she said.

Patients with previously undiagnosed OSA and EDS had greater odds of depression than did those without OSA and EDS (OR, 4.2), and had greater odds of depression than did those with either condition alone (OR, 3.5).

Further, previously diagnosed OSA and previously undiagnosed severe OSA at follow-up were significantly associated with depression onset over a 5-year period (OR, 2.1 and 2.9, respectively), Dr. Lang said.

The findings support those of prior studies that have demonstrated a link between sleep apnea and depression.

As many as 22% of those with OSA also have clinically significant depres-

Continued on following page

VITALS

Key clinical point: Patients who present for OSA or depression should be screened for both.

Major finding: Patients with previously undiagnosed OSA and EDS had greater odds of depression than did those without OSA and EDS (OR, 4.2).

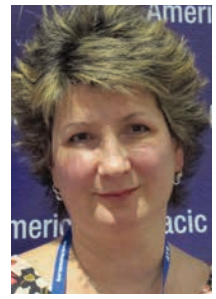
Data source: A population-based cohort study of 1,875 men.

Disclosures: Dr. Lang reported having no relevant financial disclosures.

Continued from previous page

sive symptoms, compared with 5% of the general population. Daytime sleepiness can occur in those with OSA, but not everyone with OSA reports daytime sleepiness, she said, noting that few prior studies have looked at the relationship between OSA and depression in a community-based population.

"Our study, in a large community-based sample of men, confirms a strong relationship even after adjustment for a number of other potential risk factors," she said. The mechanisms underlying the association remain unclear, but many of the symptoms of and risk factors for OSA and depression may overlap.



Altered physiology with OSA may be linked with changes that impact depression.

DR. TEODORESCU

"Sleep apnea is also associated with lower oxygen levels in the body, and this causes a range of physiological consequences, including altered inflammatory responses, hormonal stimulation, as well as neurological changes in the brain that just happen

to be in the same region of the brain that might actually impact depression, feelings of guilt, worthlessness, and suicidal tendencies," she said.

The message to clinicians based on these findings is that patients who present with symptoms of either OSA or depression should be screened for both.

"Often, I think, when people present with depression, it's easy to just assume the sleep problems are related to the depression itself ... but there may actually be benefit for the patient if both are investigated and treated," she concluded.

Dr. Mihaela Teodorescu of the University of Wisconsin, Madison, who moderated the press conference, added that additional data exist to suggest that sleep apnea leads to "more severe, and actually refractory depression," and further stressed that lack of awareness of the association can be harmful for patients.

"These people just get more antidepressants, including benzodiazepines, which are really detrimental for the obstructive sleep apnea pathogenesis, worsening depression. So it's very important for the community to be aware about sleep apnea as a potential aggravator and contributor to depression," she said.

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Asymptomatic stenosis, central apnea linked

BY BIANCA NOGRADY
Frontline Medical News

FROM CHEST

More than two-thirds of patients with asymptomatic carotid stenosis are likely have sleep apnea, according to an observational study.

The polysomnography results of 96 patients with asymptomatic extracranial carotid stenosis revealed that 69% had sleep apnea. Obstructive sleep apnea was present in 42% and central sleep apnea in 27%.

Stenosis severity was significantly associated with central sleep apnea, but not with obstructive sleep apnea. Central sleep apnea, but not obstructive sleep apnea, was associated with arterial hypertension and diabetes in those patients with asymptomatic carotid stenosis (CHEST 2015;147:1029-1036 [doi:10.1378/chest.14-1655]).

The patients' mean age was 70

years; 64 were men. Of the 96 patients, 21 had mild/moderate stenosis and 75 had severe stenosis. The frequency of arterial hypertension and diabetes mellitus was higher in the severe stenosis group than in the mild/moderate stenosis group.

The prevalence of sleep apnea was 76% in patients with severe stenosis compared with 29% in those with mild/moderate carotid stenosis.

Total apnea-hypopnea index was higher in the severe stenosis group compared with the mild/moderate stenosis group (*P* less than or equal to .009).

Increase in sleep apnea severity was based on an increase in central apnea-hypopnea index (*P* less than or equal to .001) but not in obstructive apnea-hypopnea index, reflecting an augmentation of central sleep apnea and not of obstructive sleep apnea in patients with severe compared with mild/moderate carotid stenosis.

"This vascular risk constellation seems to be more strongly connected with CSA [central sleep apnea] than with OSA [obstructive sleep apnea], possibly attributable to carotid chemoreceptor dysfunction," wrote Dr. Jens Ehrhardt and colleagues at Jena University Hospital, Germany.

No conflicts of interest were declared.

Early goal-directed therapy did not cut septic shock

BY AMY KARON
Frontline Medical News

For patients in early septic shock, goal-directed therapy based on continuously monitoring central venous oxygen saturation did not improve outcomes compared with standard care, according to a multicenter randomized trial reported in the New England Journal of Medicine and at the annual meeting of the International Society on Intensive Care and Emergency Medicine.

All-cause mortality at 90 days was 29% for both study arms, and costs of care were similar, reported Paul R. Mouncey of the Intensive Care National Audit and Research Centre, London, and his associates. The trial is the last of three planned studies of early, goal-directed therapy (EGDT), "all of which showed that EGDT was not superior to usual care," the investigators wrote (N. Engl. J. Med. 2015 Mar. 17 [doi:10.1056/NEJMoa1500896]).

Support for EGDT originated mainly from a single-center, proof-of-concept study in 2001 by Dr. Emanuel Rivers and associates, who reported lower hospital mortality and length of stay when patients in early septic shock received 6 hours of treatment aimed at optimizing oxygen transport (N. Engl. J. Med. 2001;345:1368-77).

The protocol called for continuously monitoring central venous pressure, mean arterial pressure, and central venous oxygen saturation to guide use of intravenous fluids, vasoactive drugs, and red-cell transfusions. But uptake of EGDT has been limited, and clinicians have been concerned about the validity of the results and the complexity, risks, and costs of implementing EGDT, Mr. Mouncey and his associates said.

For the study, they randomized 1,260 patients with signs of early septic shock to either EGDT or standard care. All patients received intravenous antibiotics and adequate fluid resuscitation. The EGDT group also underwent a 6-hour resuscitation protocol that included monitoring central venous oxygen saturation, with additional treatment decisions left up to the treating clinician.

In all, 29.5% of patients who received EGDT died within 90 days, as did 29.2% of patients who received standard care ($P = .90$). The EGDT group received more intravenous fluids, vasoactive drugs, and red-cell transfusions and had significantly worse organ-failure scores, more days of advanced cardiovascular support, and longer ICU stays, but had no improvement in health-related quality of life or other secondary outcomes, the researchers reported.

"On average, EGDT increased costs, and the probability that it was cost-effective was below 20%," they wrote. "Our results suggest that techniques used in usual resuscitation have evolved over the 15 years since the landmark study by Rivers et al."

The United Kingdom National Institute for Health Research health technology assessment program funded the study. Nine coauthors reported receiving grants from the NIHR. One coauthor reported grants from ImaCor and Cheetah Medical.

CRITICAL CARE COMMENTARY: Is it time to deconstruct the idea of burnout for ICU clinicians?

BY DR. LEE MORROW, FCCP

The concept of clinician burnout in the ICU is not new. Loosely defined as the physical, psychological, and emotional exhaustion of health-care providers working in high stress environments, this entity has been well documented among ICU physicians, nurses, and trainees for decades.

The overall magnitude of this problem is very real and has been reported to be as high as 60% depending on the criteria used. Burnout risk factors vary by study and clinical duties but generally include female gender, reduced job satisfaction, fewer years of clinical experience, interpersonal conflicts, and ethical decisions regarding withdrawal of care.

Burnout leads to a spectrum of counter-productive defense mechanisms and mood disorders ranging from depression, hopelessness, depersonalization, and rationalization to suspiciousness, aggression, and overt anxiety. Not surprisingly, the end result for many individuals suffering from burnout is instability of personal relationships, often extending beyond the workplace.

A recent study using meta-analysis techniques suggests that between 17% and 34% of patients continue to experience PTSD symptoms during the 7- to 12-month post-ICU period.

But what are the adverse effects of this environment on another vulnerable group of individuals who similarly struggle under the stresses inherent to the ICU— namely, our critically ill patients? Might they not suffer from a distinct but similar ICU 'burnout' phenomenon? After all, patients with serious illnesses and prolonged ICU stays certainly experience physical, psychological, and emotional exhaustion. They often struggle with dissatisfaction related to their quality of life, interpersonal conflicts, and difficult decision making regarding their own disability and/or mortality. And although the duration of these stressors is usually brief when compared with that imposed on ICU providers, the intensity of these pressures are likely magnified exponentially for critically ill patients.

Accordingly, the resulting product of ICU stress duration and intensity may not be very different for clinicians and patients.

As ICU clinicians, we are generally facile in identifying the sequelae of depression, hopelessness, rationalization, aggression, and/or anxiety in our ICU patients. But we are quick to minimize the consequences, assuming that these changes are reactive to the acute illness and are destined to resolve quickly as the patient recovers from their physical misadventure. The increasingly evident truth, however, is that these patients' encounters with the ICU have the alarming potential for prolonged consequences that are eerily similar to the syndrome of burnout that the ICU inflicts on many health-care providers.

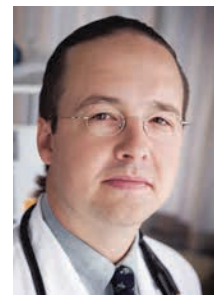
Although only in the infancy of its elucidation, the effects of ICU care on survivors of critical illness are beginning to come into sharper focus.

Our early evaluations suggested that the incidence of posttraumatic stress disorder (PTSD) shortly after critical illness approached 50% (Jones et al. *Crit Care Med*. 2003;31[10]:2456). Subsequent investigators estimate that while many ICU patients have isolated PTSD symptoms, many of which overlap with the burnout syndrome we have already discussed, overt PTSD that persists with a long-term horizon occurs in between 10% and 20% of ICU survivors (Davydov et al. *Gen Hosp Psychiatry*. 2013;35[3]:226).

Risk factors for PTSD in the ICU cohort appear to include pre-existing psychiatric disease, younger age, female gender, ICU delirium, vivid ICU memories, and delusions or hallucinations. There is a disquieting degree of overlap between this list of PTSD risk factors and the variables previously reported as predisposing to ICU clinician burnout.

A recent study using meta-analysis techniques has further refined our appreciation of the prevalence of "clinically important posttraumatic stress disorder symptoms" (Parker et al. *Crit Care Med*. 2015;43[5]:1121). This systematic literature review and rigorous analysis suggest that between 17% and 34% of patients continue to experience PTSD symptoms during the 7 to12 month post-ICU period (depending on where we set the bar for clinically important symptoms).

This syndrome, while not meeting strict PTSD-defining criteria, has been associated with a reduced quality of life, and one could easily consider this to be an equivalent of ICU burnout.


DR. MORROW

Equally distressing, but less well elucidated, is the effect the ICU experience can have on the individuals who surround ICU survivors during their more prolonged recovery from intensive care.

A timely study of informal caregivers for survivors of critical illness – typically their family members – found that up to 29% of the patients' caregivers suffer from depressive symptoms 1 year after critical illness (Haines et al. *Crit Care Med*. 2015;43[5]:1112). This estimate is surprisingly similar to the rates of PTSD symptoms in the ICU survivors and is in line with ICU provider burnout rates.

So, perhaps there is yet another analogous form of ICU burnout – one that afflicts family members? In retrospect, this should not be surprising given that these individuals also suffer distinct forms of physical, psychological, and emotional exhaustion.

A timely study of informal caregivers for survivors of critical illness – typically their family members – found that up to 29% of the patients' caregivers suffer from depressive symptoms 1 year after critical illness.

Given these observations, it is apparent that the ICU is a double-edged sword, one that provides remarkable degrees of physical healing for many people, yet causes profound emotional harm in others. However, these entities have remained compartmentalized until this point in time: burnout occurs only in the health-care providers, PTSD is the domain of the patients, and depression is seen among the caregivers.

But perhaps these apparently separate entities are actually interconnected and represent points on the bigger spectrum of critical illness-associated burnout (for lack of a better term). Although the data regarding risk factors for burnout/PTSD/depression are not robust, there is significant overlap of these items (gender, age/experience, satisfaction domains, degrees of conflict, emotional decision making) among providers, patients, and caregivers. Is this yet another signal that these entities may be more similar than they are different?

At the end of the day, perhaps we have even more in common with our ICU patients and their caregivers than we have previously recognized.

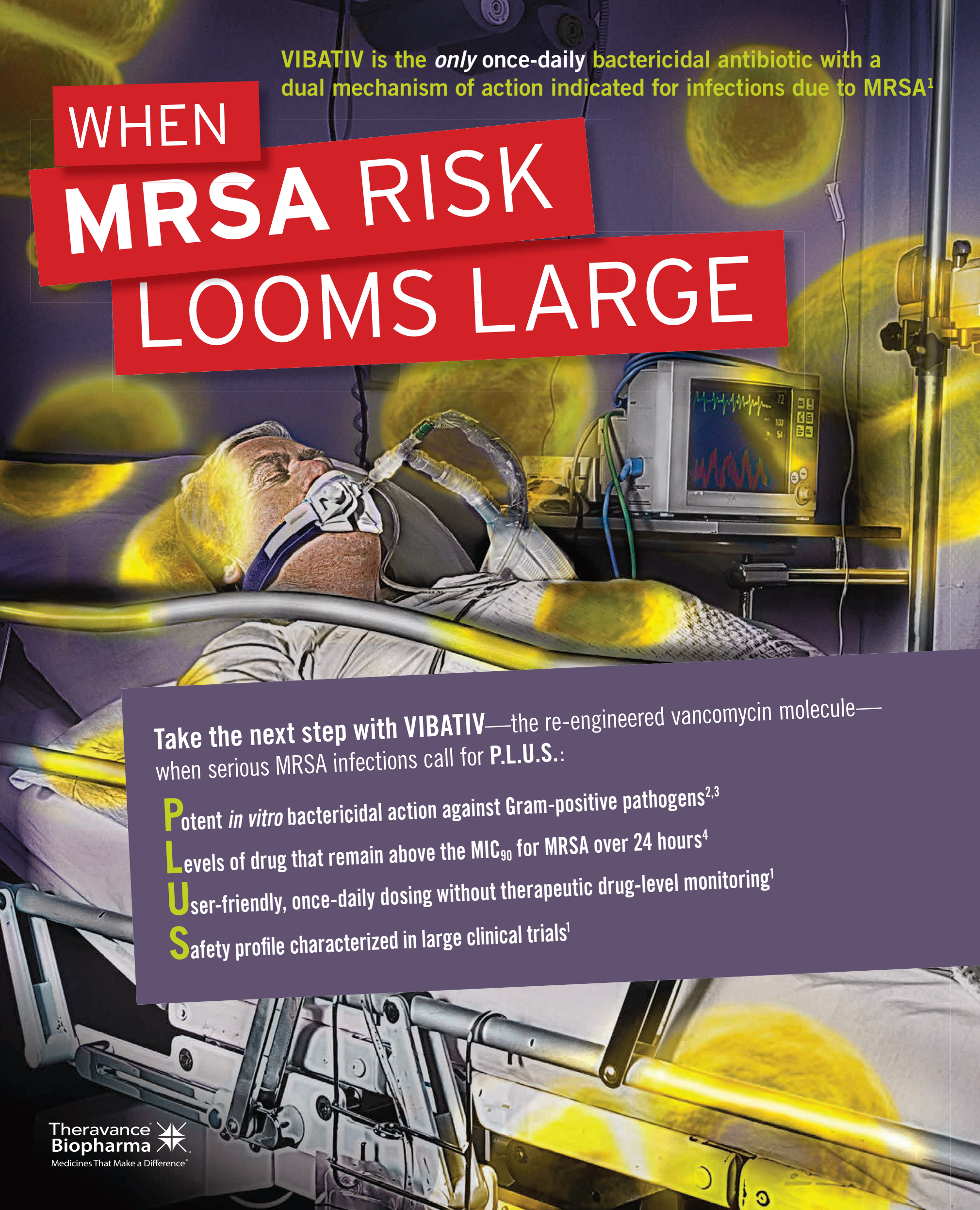
A critically important reason to better understand the interconnectedness of these entities (or lack thereof) lies with our ability to eventually provide meaningful prevention strategies.

Effective interventions for reducing health-care provider burnout have included resilience training and rotating responsibilities to mandate tours of duty outside the ICU are interspersed with brief (less than 2 weeks) ICU stretches. In the ICU patient population, a daily care diary has been associated with a significant reduction in PTSD symptoms. The data are scant regarding prevention of caregiver depression but one small study of journaling and reflection suggests benefit. To date, no strategy with efficacy in one cohort has been extrapolated to another.

As such, we have a significant task ahead of us. We need to better understand the ICU-related burnout/PTSD/depression syndrome and to delineate its common ground for clinicians, patients, and families.

With ongoing evaluation and reflection, we will ultimately evolve ICU care to the point where interrelated strategies are employed that allow us to effectively heal patients physically while avoiding this critical care burnout syndrome that insidiously affects us all.

Dr. Morrow is Section Editor of Critical Care Commentary.



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INDICATION

VIBATIV is indicated for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates). VIBATIV should be reserved for use when alternative treatments are not suitable.

VIBATIV is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates)
- *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), or
- *Enterococcus faecalis* (vancomycin-susceptible isolates only)

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. VIBATIV may be initiated as empiric therapy before results of these tests are known. To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Available in two strengths: 250 mg and 750 mg[1]

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IMPORTANT SAFETY INFORMATION

Mortality
Patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk.

Nephrotoxicity
New onset or worsening renal impairment occurred in patients who received VIBATIV. Renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction and in patients who received concomitant medications known to affect kidney function.

Monitor renal function in all patients receiving VIBATIV prior to initiation of treatment, during treatment, and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed.

Fetal Risk
Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment.

Contraindication
VIBATIV is contraindicated in patients with a known hypersensitivity to the drug.

Hypersensitivity Reactions
Serious and potentially fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin.

Geriatric Use
Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

Infusion Related Reactions
VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause "Red-man Syndrome"-like reactions including: flushing of the upper body, urticaria, pruritus, or rash.

QTc Prolongation
Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. In a study involving healthy volunteers, VIBATIV prolonged the QTc interval. Use of VIBATIV should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy.

Most Common Adverse Reactions
The most common adverse reactions (greater than or equal to 10% of patients treated with VIBATIV) were taste disturbance, nausea, vomiting, and foamy urine.

For full Prescribing Information, including Boxed Warning and Medication Guide in the US, please visit www.VIBATIV.com.

References: 1. VIBATIV® (telavancin) Prescribing Information. Theravance Biopharma Antibiotics, Inc. March 2014. **2.** Draghi DC, et al. Comparative surveillance study of telavancin activity against recently collected Gram-positive clinical isolates from across the United States. *Antimicrob Agents and Chemother.* 2008;52:2383-2388. **3.** Draghi DC, et al. *In vitro* activity of telavancin against recent Gram-positive clinical isolates: results of the 2004-05 Prospective European Surveillance Initiative. *J Antimicrob Chemother.* 2008;62:116-121. **4.** Data on file. Theravance Biopharma Antibiotics, Inc.

VBT 00046-04 August 2014

Ultrasound predicts trauma thoracotomy survival

BY KARI OAKES
Frontline Medical News

SAN DIEGO – The few trauma patients who will survive a high-risk thoracotomy procedure for cardiac arrest can be predicted by the presence of cardiac motion as detected by a quick and inexpensive bedside ultrasound, the results of a prospective study conducted at a level I trauma center showed.

Focused assessment with sonography in trauma (FAST) was 100% sensitive and 62% specific in predicting those who would survive or be eligible for organ donation after receiving a resuscitative thoracotomy for traumatic cardiac arrest, said Dr. Kenji Inaba of the department of surgery at the University of Southern California Medical Center in Los Angeles.

Resuscitative thoracotomy, said Dr. Inaba, is a salvage procedure performed after cardiac arrest. It is a "high-risk, resource-intensive procedure, with a low quantitative yield. And yet, patients do survive."

VITALS

Key clinical point: Trauma arrest victims who will survive resuscitative thoracotomy can be predicted using focused assessment with sonography in trauma.

Major findings: FAST was 100% sensitive for detecting survivors after resuscitative thoracotomy for traumatic cardiac arrest.

Data source: A prospective series of 187 trauma patients in cardiac arrest undergoing resuscitative thoracotomy from 2010 to 2014 at a level I trauma center.

Disclosures: The authors reported no relevant financial disclosures.

Previous retrospective studies found that of those receiving resuscitative thoracotomy for traumatic arrest, 7.4% survived, with more than 90% of survivors retaining neurologic function; an additional 4.2% of recipients were potentially eligible for organ donation.

Thus, a tool to identify potential survivors among those who present in post-traumatic cardiac arrest would help avoid unnecessary use of a procedure with such risks and resource burdens.

FAST, an inexpensive procedure that is standard for other indications in trauma, has been effective in identifying potential survivors in thoracotomy for nontrauma cardiac arrests.

The technique "has near-universal availability, can be performed immediately at the bedside without moving the patient, and yields real-time results with no radiation involved," Dr. Inaba said at the annual meeting of the American Surgical Association.

For the current prospective study, the specific aim was to examine the ability of FAST to differentiate survivors and potential organ donors from those who would not survive resuscitative thoracotomy among those presenting in traumatic cardiac arrest.

Dr. Inaba and his associates ex-

Continued on following page

Severe sepsis definition excluded at-risk patients

BY AMY KARON
Frontline Medical News

Requiring patients to meet at least two of the criteria for systemic inflammatory response syndrome (SIRS) excluded one in every eight patients with infection and organ failure, and did not help predict mortality, according to a large multicenter retrospective study.

Patients with SIRS-negative severe sepsis had "substantial mortality and … epidemiologic characteristics and changes that were essentially identical to those of patients with SIRS-positive severe sepsis," wrote Dr. Kirsi-Maija Kaukonen at Monash University in Melbourne, and her associates.

"Our findings challenge the sensitivity, face validity, and construct validity of the rule regarding two or more SIRS criteria in diagnosing or defining severe sepsis in patients in the ICU," the researchers wrote in a report in the New England Journal of Medicine, which was published simultaneously with their presentation at the annual meeting of the International Society on Intensive Care and Emergency Medicine.

Since 1992, the American College of Chest Physicians and the Society of Critical Care Medicine have defined severe sepsis as suspected or proven infection, organ failure, and signs that meet at least two SIRS criteria. But affected elderly patients and those who take medications that affect heart rate, respiratory rate, or body temperature might not meet the definition, the researchers said (*N. Eng. J. Med.* 2015 [doi:10.1056/NEJMoa1415236]).

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VITALS

Key clinical point: Defining severe sepsis as meeting at least two SIRS criteria excluded patients with infection and organ failure, and did not help predict mortality.

Major finding: The consensus definition excluded one in every eight patients with infection and organ failure.

Data source: Multicenter retrospective study of 109,663 ICU patients with infection and organ failure.

Disclosures: The Australian and New Zealand Intensive Care Research Centre funded the study. Dr. Kaukonen reported receiving grant support from the Academy of Finland. The other authors declared no relevant conflicts of interest.

To test the validity of the definition, the researchers retrospectively studied 109,663 patients who had infection and organ failure that was treated over 14 years at 172 intensive care units in Australia and New Zealand.

About 88% of the patients had SIRS-positive severe sepsis, while 12% had SIRS-negative severe sepsis.

The two groups had similar characteristics and declines in mortality (for SIRS-positive patients, a drop in mortality from 36% to 18%; for SIRS-negative patients, a decrease in mortality from 27% to 9%; $P = .12$ for between-group difference), according to the investigators.

The odds of mortality rose linearly by about 13% for each additional SIRS criterion (odds ratio, 1.13; 95% confidence interval, 1.11-1.15; $P < .001$), but there was no additional increase in mortality risk at the two-criteria threshold.

Rates of discharge to rehabilitation and long-term care facilities also were similar between the two groups of patients.

Applying the two-SIRS criterion within 24 hours of ICU admission – the most common time window for recruitment into sepsis trials – would exclude about one in every eight patients with infection and organ failure, the investigators concluded.

"These patients have substantial mortality and their epidemiologic data are identical to those of patients with classic SIRS-positive severe sepsis, which suggests that these two groups represent different clinical phenotypes of the same process," the researchers concluded.

Continued from previous page

amined the predictive value of cardiac motion and the presence of pericardial fluid for survival, as well as the adequacy of the FAST study for each patient.

The single-center study, conducted from 2010 to 2014, enrolled 187 patients (mean age, 31; 85% male) presenting in traumatic arrest who received resuscitative thoracotomy in the emergency department and also received a FAST.

The ultrasound scans were performed by emergency medicine residents under direct faculty supervision.

Of the 187 patients studied, 6 (3.2%) survived, 3 (1.6%) became organ donors, and 178 (95%) died but were not organ donor eligible.

Cardiac motion was detected by FAST in 54 (29%) individuals in the total study population; among these were all nine of the survivors and donors, yielding a sensitivity of 100% and a specificity of 74% for survival ($P < .001$).

All 16 of the patients with pericardial fluid detected by FAST died, as did all 7 patients in whom the study was deemed inadequate.

In other words, Dr. Inaba said, "no cardiac motion equals no survival."

If thoracotomies had been performed only on patients in the study group who had cardiac motion on FAST, more than half of the unsuccessful resuscitative thoracotomies would have been avoided, Dr. Inaba noted.

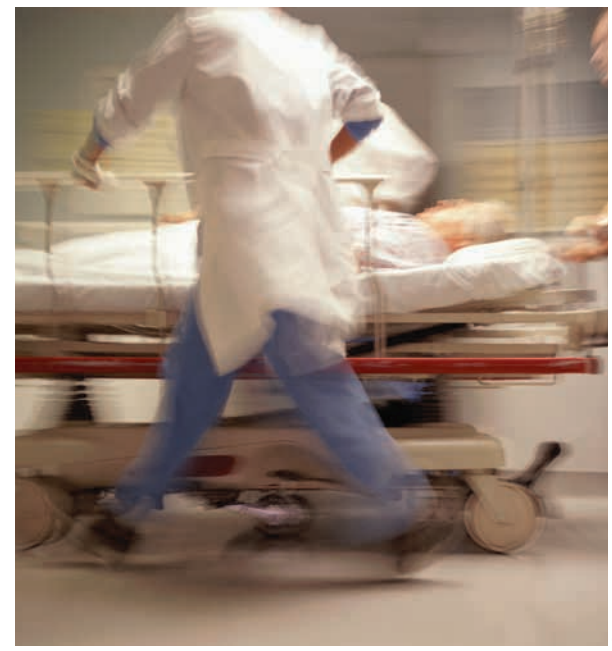
The study, he said, has particular application for lower-volume trauma centers that must carefully weigh the prolonged use of limited resources required in a resuscitative thoracotomy.

Dr. David Spain, chief of trauma and critical care surgery at Stanford (Calif.) University, asked whether the study captured the mechanism of injury.

Though the study did not do so, said Dr. Inaba, he and his colleagues realized that a subset of the patients who went immediately to the operating room was not included in the study, which is a potential limitation of their research. This group of patients included those who had a penetrating cardiac injury – a possible reason, he said, why none of the patients among the survivors had a cardiac injury.

The authors reported no relevant financial disclosures.

The complete manuscript of this study and its presentation at the American Surgical Association's 135th Annual Meeting, April 2015, in San Diego, California, are anticipated to be published in the Annals of Surgery pending editorial review.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Anticipation runs high for coming megatrials

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – Preventive cardiovascular medicine will get "a big boost" from ongoing major randomized controlled trials due to report results during the next several years, Dr. Eric D. Peterson predicted at the annual meeting of the American College of Cardiology.

He presented an overview of eagerly anticipated clinical trials approaching completion in three of the hottest areas of research in general cardiology: new cardiovascular prevention agents and strategies; innovative health policy initiatives; and optimal antithrombotic regimens across the range of chronic coronary artery disease, peripheral vascular disease, patients with atrial fibrillation who've undergone percutaneous coronary intervention, and cerebrovascular disease.

Dr. Peterson is executive director of the Duke Clinical Research Institute (DCRI), a major player in some of these studies. To gain additional perspective regarding what's in store, he consulted a who's who list of eminent American cardiology clinical trialists as to what's going to be big in 2016-2017 and shortly beyond.

One thing's clear looking out at the research horizon: Megatrials enrolling tens of thousands of patients to answer key clinical questions are not a thing of the past.

Far from it.

Cardiovascular prevention

Exciting pivotal phase III cardiovascular prevention trials are well underway in the areas of lipid modification, diabetes, and hypertension. In addition, the possible preventive effect of vitamin D and omega-3 free fatty acid supplementation seen in hypothesis-generating epidemiologic studies is finally being put to a definitive test in a 26,000-subject randomized trial known as VITAL (the Vitamin D and omega-3 trial).

Lipids: All eyes are on ongoing pivotal phase III randomized clinical outcome trials of three monoclonal antibodies that inhibit proprotein convertase subtilisin kexin type 9 (PCSK9): the 22,500-patient FOURIER trial of evolocumab, which includes 9,000 patients older than 65 years; the 18,000-patient ODYSSEY Outcomes trial of alirocumab; and the SPIRE-1 and SPIRE-2 trials of bococizumab totaling 18,300 patients.

In phase II studies, these agents have generated enormous excitement, because they safely achieve unprecedented LDL lowering, with early hints of improved clinical outcomes beyond what's achievable with today's drugs, noted Dr. Peterson, professor of medicine at Duke University in Durham, N.C.

CETP inhibitors: The cholesteryl ester transfer protein inhibitors torcetrapib and dalcetrapib flamed out in clinical trials because of safety concerns and lack of clinical benefit. But pivotal phase III trials of two other CETP inhibitors are well underway: anacetrapib, which is the focus of the 30,000-patient REVEAL trial; and evacetrapib, featured in the 11,000-patient ACCELERATE trial. The CETP inhibitors simultaneously boost HDL while reducing LDL.

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

All eyes are on ongoing pivotal phase III randomized clinical outcome trials of three monoclonal antibodies that inhibit PCSK9, Dr. Eric D. Peterson said.

Diabetes: The search continues for new drugs that not only enhance diabetes control but also improve cardiovascular outcomes, or at the very least are safe in diabetes patients with coronary disease.

Next up is the nearly 15,000-patient Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), coordinated by the DCRI and University of Oxford. It's due to be presented in June at the annual meeting of the American Diabetes Association in Boston. Trials of other dipeptidyl peptidase-4 inhibitors have shown evidence of an increased risk of heart failure, specifically with saxagliptin in the SAVOR-TIMI 53 trial and alogliptin in EXAMINE, so a lot is riding on TECOS.

The glucagon-like peptide-1 (GLP-1) agonists are under study in cardiovascular event-driven randomized clinical trials collectively totaling more than 33,000 patients with type 2 diabetes. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL), also coordinated by the DCRI and University of Oxford, includes 14,000 randomized patients. Other major trials of GLP-1 agonists are ELIXA (lixisenatide), LEADER (liraglutide), and REWIND (dulaglutide).

In addition, ongoing phase III trials of sodium glucose cotransporter 2 (SGLT-2) inhibitors with cardiovascular endpoints include the Canagliflozin Cardiovascular Assessment Study (CANVAS) and a 7,000-patient study of empagliflozin known as EMPA-REG OUTCOME.

Hypertension: The Systolic Blood Pressure Intervention Trial (SPRINT) is an NIH-funded, randomized trial

It's remarkable that physicians still don't know the right dose of aspirin to use, even though the drug has been around since 1897. The answer will come from the ADAPTABLE eTrial.

designed to finally answer a question bothering physicians for years: What's the right amount of blood pressure lowering?

Nearly 9,400 high-risk patients with clinical or subclinical cardiovascular disease have been randomized to a target systolic blood pressure of less than 120 mm Hg, compared with less than 140 mm Hg. The primary composite endpoint is cardiovascular death, nonfatal MI or stroke, or hospitalization for acute coronary syndrome. Secondary endpoints focus on cognitive impairment, dementia, and rates of progression of chronic kidney disease. Results are expected in 2018.

Vitamin D: The VITAL trial, also sponsored by the NIH, has randomized 25,875 initially healthy men and women to 2,000 IU of vitamin D_3 per day or placebo, and further randomized them to 1 g/day of omega-3 fatty acids or placebo. Key endpoints are total cancers, MI, stroke, and cardiovascular death. Results are coming in 2017.

Optimal antithrombotic therapy

Chronic coronary artery disease: It's remarkable that physicians still don't know the right dose of aspirin to use, even though the drug has been around since 1897. The answer is finally on the way. It will come from the ADAPTABLE eTrial, the first comparative effectiveness research project funded by the Patient-Centered Outcomes Research Institute (PCORI).

Twenty thousand U.S. patients with known atherosclerotic cardiovascular disease and at least one extra risk factor will be randomized to daily aspirin at 81 mg or 325 mg and followed for a maximum of 30 months. The primary efficacy endpoint is all-cause mortality, nonfatal MI, or nonfatal stroke. The primary safety endpoint is major bleeding.

This is a groundbreaking innovative study: It's a 20,000-patient trial budgeted at a mere $10 million – peanuts in the world of megatrials. By comparison, the NIH-funded SPRINT hypertension trial includes less than half as many patients, yet the price tag is $114 million.

The bargain-basement cost of the aspirin trial is possible because follow-up will be via electronic medical records and claims data provided every 3 months by 29 health data networks participating in PCORI's National Patient-Centered Clinical Research Network (PCORnet). The aspirin study is sort of a shakedown cruise for an exciting new cost-effective approach to conducting comparative effectiveness research.

"This study could be a game changer," Dr. Peterson declared. "Whether you think the research question is important or not, the ability to utilize electronic health records in long-term patient follow-up in ran-

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domized trials will be revolutionary in terms of answering key clinical questions cost effectively."

Peripheral vascular disease: In search of the antithrombotic regimen that optimizes limb salvage while minimizing vascular event rate, the EUCLID trial has randomized 13,500 patients with symptomatic peripheral artery disease to ticagrelor at 90 mg BID or clopidogrel at 75 mg/day. Follow-up will be for 18 months, with the primary endpoint a composite of cardiovascular death, nonfatal MI, or ischemic stroke.

'There's the possibility that insurers can be persuaded to pay for medications and basically give them away as a means of ultimately resulting in better outcomes for patients and lower costs.'

Atrial fibrillation patients who undergo coronary stent placement: The 2,100-patient PIONEER AF-PCI study, now recruiting, is evaluating different combinations of rivaroxaban in various dosing regimens coupled with clopidogrel, warfarin, and/or aspirin.

Stroke: The SOCRATES trial is recruiting 9,600 patients with acute ischemic stroke or high-risk transient ischemic attack to be randomized within 24 hours to ticagrelor at 90 mg BID or aspirin at 100 mg/day. As with PIONEER, results from SOCRATES are anticipated next year.

Health policy and implementation

The ARTEMIS study poses the question of whether providing a guideline-directed medication gratis will improve patient adherence and/or clinical outcomes.

Some 9,000 high-cardiovascular-risk patients at 300 sites are being randomized to free ticagrelor or clopidogrel – no copay – for 1 year or to usual care. Outcomes include choice of medication, adherence, and major adverse cardiovascular events.

"If this works, there's the possibility that insurers can be persuaded to pay for medications and basically give them away as a means of ultimately resulting in better outcomes for patients and lower costs," Dr. Peterson said.

IMPACT AF is an international quality improvement project aimed at improving the use of oral anticoagulation therapy in high-risk patients with atrial fibrillation in Argentina, Brazil, China, India, and Romania. Participating centers will be randomized to receive a provider education and feedback program or not. The primary outcome is a change from baseline through year 1 in the proportion of patients with atrial fibrillation taking an oral anticoagulant.

In summing up the state of research in general cardiology, Dr. Peterson observed, "The way we do trials is changing. The size of the studies is changing. But ultimately, we will find better ways to treat patients, and perhaps we can find better ways to encourage patients to take their medications long term."

Dr. Peterson reported serving as a consultant to AstraZeneca Boehringer Ingelheim, Genentech, Janssen, and Sanofi, and receiving research funding from Eli Lilly and Janssen.

bjancin@frontlinemedcom.com

Once-daily inhaled fluticasone-vilanterol approved

BY ELIZABETH MECHCATIE
Frontline Medical News

Fixed-dose combinations of the inhaled corticosteroid (ICS) fluticasone and the long-acting beta-agonist (LABA) vilanterol have been approved by the Food and Drug Administration for treating asthma in adults, the manufacturer, GlaxoSmithKline, announced. Vilanterol, as part of the combination product, is the first new LABA approved for asthma in 15 years and fluticasone-vilanterol is the first once-daily inhaled ICS-LABA combination approved for asthma.

Two strengths have been approved, 100 mcg or 200 mcg of fluticasone with 25 mcg of vilanterol, administered once a day with a dry powder inhaler, for people 18 years and older, according to the company's statement. The products are marketed as

Breo Ellipta. In 2013, the 100/25 mcg dose was approved for COPD.

The company had filed for approval for treating asthma in adolescents aged 12-17 years who were studied in the same trials as adults, but the FDA did not approve the product in this age group. In the statement, GSK said the FDA issued a "complete response" letter for the younger age group, "stating that the data submitted do not show adequate risk-benefit to support the approval in these patients," and that more data are needed.

The FDA decision reflects the recommendations of the FDA's Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, which, at a meeting on March 19, voted 16-4 that the efficacy and safety data supported the approval of both proposed doses in adults. But the panels voted 19-1 that the data did not support approval for adolescents.

As with other LABA products, the prescribing information for Breo Ellipta includes a boxed warning about the risk of asthma-related deaths associated with LABAs. Unlike the LABAs salmeterol and formoterol, vilanterol is not approved for use as a single agent. Fluticasone (100 mcg and 200 mcg) is approved for asthma.

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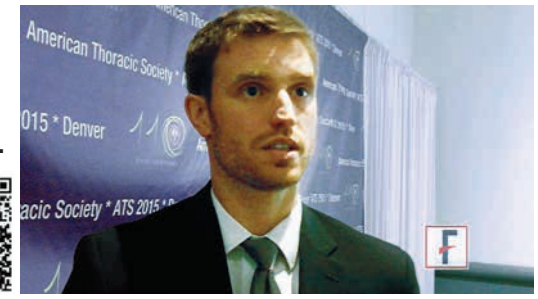
e-Cigarettes linked to toxicities

DENVER – The higher the power of an e-cigarette, the higher the concentrations of potentially hazardous substances the device produces, including acetaldehyde, acrolein, and formaldehyde. At an international conference of the American Thoracic Society, Dr. Daniel Sullivan, of the University of Texas Southwestern Medical Center., presented data showing e-cigarettes, under test conditions, produce formaldehyde levels similar to those seen with tobacco cigarettes.

—Doug Brunk

Daniel Sullivan reported on study results indicating e-cigarettes emit toxic chemicals. Scan to watch the video.



Doug Brunk/Frontline Medical News

Aclidinium/formoterol bests salmeterol/fluticasone

BY DOUG BRUNK
Frontline Medical News

DENVER – In patients with stable COPD, a fixed-dose combination of aclidinium/formoterol provided significantly greater improvements in bronchodilation compared with a fixed-dose combination of salmeterol/fluticasone, with equivalent benefits in symptom control and reduction in exacerbation risk, a randomized, controlled trial showed.

"This study will be important to building further evidence for the clinical use of inhaled long-acting muscarinic antagonist (LAMA) and long-acting beta agonist (LABA) fixed-dose combinations as a valuable tool in the treatment armamentarium for COPD," Dr. Claus Vogelmeier said in an interview at an international conference of the American Thoracic Society.

Continued on following page

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"While there have been other positive studies showing benefits in LAMA/LABA fixed-dose combinations over the specific ICS/LABA fixed-dose combination of salmeterol/fluticasone, this is the first head-to-head study that compares the efficacy and safety of aclidinium/formoterol with salmeterol/fluticasone in COPD patients," he said.

For the phase III study, Dr. Vogelmeier, professor of medicine and head of the pulmonary division at Marburg University Hospital, Germany, and his associates randomized 933 symptomatic COPD patients 1:1 to 24 weeks of treatment with aclidinium/formoterol 400/12 mcg twice daily via Genuair/Pressair (AstraZeneca) or salmeterol/fluticasone 50/500 mcg twice daily via Accuhaler (GlaxoSmithKline).

The primary efficacy endpoint was peak forced expiratory volume in 1 second (FEV_1) at week 24. Other efficacy endpoints included peak FEV_1 at each visit, Transition Dyspnea Index (TDI) focal score and COPD Assessment Test (CAT) score at week 24, and the proportion of patients who experienced at least one exacerbation defined by health care resource utilization (HCRU) or identified using the Exacerbations of Chronic Pulmonary Disease Tool (EXACT)..

Of the 933 patients, 788 (85%) completed the study. Their mean age was 63 years and 65% were male. Peak FEV_1 was significantly greater with aclidinium/formoterol than salmeterol/fluticasone after the first dose on day 1, an improvement that was maintained at week 24 (treatment differences of 83 mL and 93 mL, respectively; *P* less than .0001).

These data indicate a new option for LAMA/LABA fixed-dose therapy in symptomatic COPD.

DR. VOGELMEIER

Improvements in TDI focal score at week 24 were similar in both groups (a mean of 1.9 for both), and there were no significant differences in CAT total score at week 24 (15.8 vs. 16.1). The proportion of patients with one exacerbation or more was comparable based on HCRU (odds ratio .95) or EXACT (OR .94).

The incidence of adverse events was similar among the aclidinium/formoterol and the salmeterol/fluticasone groups (50% vs. 57%, respectively), as were serious adverse events, (7.5% vs. 7.1%), and adverse events leading to study discontinuation (5.4% vs. 7.3%). Adverse events related to inhaled corticosteroid use, including pneumonia and osteoporosis/osteopenia, were more common in patients receiving salmeterol/fluticasone than in patients receiving aclidinium/formoterol (10.7% vs. 4.3%).

"These data offer physicians a new perspective and option for treating symptomatic patients at a time when the role of LAMA/LABA fixed-dose combinations is being increasingly recognized in the management of symptomatic COPD," he said.

The study was funded by Almirall, Barcelona, Spain, and Forest Laboratories, a subsidiary of Actavis. Dr. Vogelmeier disclosed ties with Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Janssen, Mundipharma, Novartis, and Takeda.

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PULMONARY PERSPECTIVES: Targeted therapy for advanced NSCLC

BY DR. TRISHALA MEGHAL
AND DR. KEVIN BECKER

Dramatic responses to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were first observed in select patients with advanced lung adenocarcinoma over 10 years ago. Since that time, targeted therapy has become the preferred first-line treatment for patients with EGFR and anaplastic lymphoma kinase (ALK) mutations. In addition, patients are often treated with sequential lines of targeted therapy as the repertoire of available agents expands. Moreover, an increasing number of patients with less common oncogenic driver mutations have targeted therapy options based on reports of successful genotype-directed treatment in the literature.


DR. MEGHAL


DR. BECKER

Oncogene addiction

A majority of lung adenocarcinomas exhibit dependence on a single oncogenic protein or driver mutation for sustaining growth and proliferation. This phenomenon, termed oncogene addiction, renders these tumors sensitive to drugs that inhibit the activity of the altered oncogene and is the theoretical basis of targeted therapy (Weinstein. *Science.* 2002;297[5578]:63). While targeted therapy has been successfully integrated into the treatment of many malignancies, including breast cancers, sarcomas, and leukemias, the diversity of driver mutations in lung cancer is unique. The Lung Cancer Mutation Consortium (LCMC) analyzed samples from 1,007 patients with lung adenocarcinomas for 10 driver mutations and found an oncogenic driver in 64% of patients. Since that time, additional driver mutations have been identified. Importantly, the median survival observed in the LCMC study was significantly better in those patients who received genotype-directed therapy as compared with those who did not (Kris et al. *JAMA.* 2014;311[19]:1998).

EGFR-mutated lung cancer

The first successful targeted therapies for lung cancer were the EGFR TKIs erlotinib and gefitinib. EGFR is a cell surface receptor tyrosine kinase that, when activated, leads to cell survival and proliferation. Mutations are observed in 15% of lung adenocarcinoma in the United States and are more common in patients with Asian ethnicity, female gender, and lack of smoking history. The most commonly found mutations are deletions in exon 19 and point mutations in exon 21. Both mutations result in constitutive activation of the receptor and are associated with sensitivity to the small molecule inhibitors erlotinib, gefitinib, and afatinib. Recognition of the dependence of EGFR-mutated lung cancers on EGFR signaling laid the groundwork for multiple randomized trials comparing first-line EGFR TKIs to standard platinum doublet chemotherapy. In each case, EGFR TKIs produced superior response rates (RR) and progression-free survival (PFS) with lower rates of serious toxicity (Sequist et al. *J Clin Oncol.* 2013;31[27]:3327; Zhou et al. *Lancet Oncol.* 2011;12[8]:735; Mok et al. *N Engl J Med.* 2009;361[10]:947). Based on these results, the National Comprehensive Cancer Network (NCCN) recommends EGFR inhibitors as initial therapy in patients with advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC) with sensitizing EGFR mutations.

ALK-mutated lung cancer

ALK is the second most common oncogenic driver for which targeted therapy has become the standard of care in lung cancer. Most often, mutations occur as a short inversion in chromosome 2p where the ALK gene is fused with the echinoderm microtubule-associated protein like 4 (EML4) gene. The EML4-ALK fusion protein is a constitutively active kinase that drives cell growth. Crizotinib is a multitargeted small molecule inhibitor of ALK, ROS1, and MET. It was compared in phase 3 randomized controlled trials with standard second line (PROFILE 1007) and first-line chemotherapy (PROFILE 1014). Crizotinib not only improved RR and PFS but also improved lung cancer symptoms and quality of life when compared with chemotherapy (Shaw et al, *N Engl J Med.* 2013;368[25]:2385; Solomon et al. *N Engl J Med.* 2014;371[23]:2167. Based on these trials, crizotinib is the recommended first-line therapy in patients with ALK-positive NSCLC.

Uncommon driver mutations

Multiple, less common driver mutations have also been validated as therapeutic targets. ROS1 is a receptor tyrosine kinase of the insulin receptor family that is mutated in 1% to 2% NSCLC. In a prospective study of 50 patients with ROS1 rearrangement, 72% of patients responded to crizotinib, and the duration of response far exceeded that expected with conventional chemotherapy (Shaw et al. *N Engl J Med.* 2014;371[21]:1963). BRAF is a downstream signaling mediator of KRAS that activates the MAP kinase pathway and is mutated in 1% to 3% of NSCLC. In a phase 2 study of patients with BRAF V600E mutations, patients treated with the BRAF inhibitor vemurafenib had a disease control rate of 56% (Peters et al. *J Clin Oncol.* 2013;31[20]:341). MET, a transmembrane tyrosine kinase receptor, is frequently dysregulated in tumor cells via elevated expression with or without gene amplification. There are case reports of responses to crizotinib in patients with MET amplification, and studies of crizotinib and cabozantinib in patients with MET amplification or mutation are underway. Fusions involving receptor tyrosine kinase RET gene have been identified in 1% to 2% of NSCLC, and there are case reports of responses to the RET kinase inhibitors vandetinib and cabozantinib. Mutations in HER2, an important oncogene in breast cancer, have been reported to respond to the HER2 TKI afatinib. While each of these driver mutations are individually infrequent, in aggregate, they represent a substantial fraction of lung cancer patients whose limited treatment options may be expanded to include targeted therapies.

Next generation tyrosine kinase inhibitors

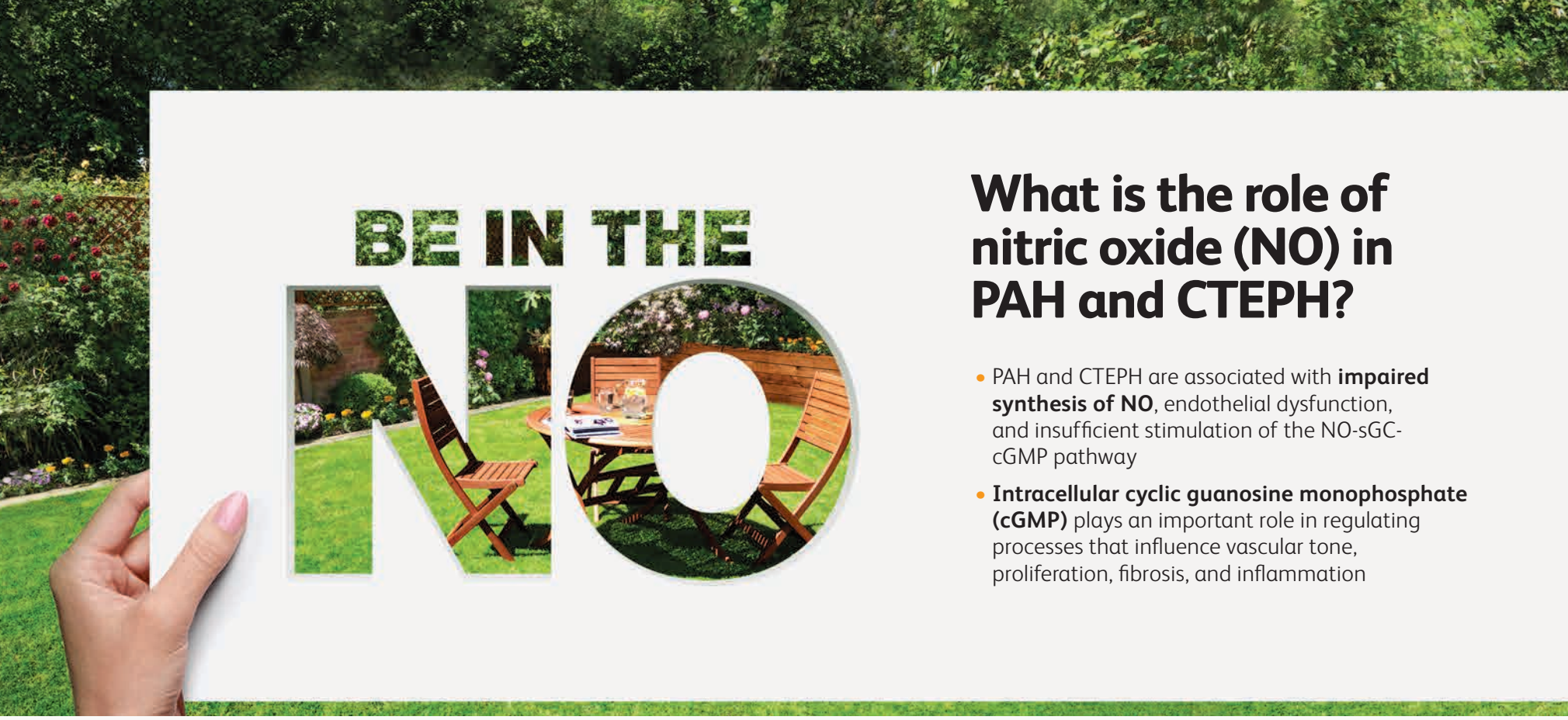
With the superiority of targeted therapy over standard chemotherapy now well-established in EGFR- and ALK-mutated lung cancers, focus has shifted to developing superior TKIs. The second generation ALK inhibitor ceritinib was recently FDA-approved for patients whose disease has progressed on crizotinib. Ceritinib is approximately 20 times more potent than crizotinib and produced responses in 56% of patients with crizotinib-resistant disease. In patients whose disease has progressed on the currently available EGFR inhibitors, a secondary mutation, T790M, can be identified in approximately 60% of tumor biopsies and mediates resistance by reactivating EGFR signaling. Rociletinib (CO-1686) and AZD9291 are third generation EGFR TKIs that not only inhibit the commonly mutated forms of EGFR but also inhibit those bearing the T790M resistance mutation. Furthermore, these drugs are more mutation-specific, showing less inhibition of the wild type EGFR receptor that is responsible for the rash and GI toxicity seen with other EGFR inhibitors. These novel TKIs are first being used as second-line treatment but may supplant the currently available TKIs as initial treatment in the future.

Molecular testing

The advanced molecular characterization of lung adenocarcinoma requires interdisciplinary cooperation between the physician performing the diagnostic procedure, the pathologist, and the oncologist for acquisition of adequate tissue and its judicious use for molecular analysis. The earliest approaches to molecular diagnostic testing involved a combination of assays that each interrogated genomic changes involving a specific gene such as Sanger sequencing, immunohistochemistry, and FISH. This one gene-one test strategy was most suitable when there were few genes to test. As the number of actionable genomic alterations increases, the amount of tissue required to carry out these tests is also increasing. Multiplex testing, along with standard FISH assays, has been successful in comprehensive genotyping but fails to detect gene rearrangements. Next generation sequencing can detect several hundreds of cancer-related genes in a single test. The NCCN guidelines strongly recommend using multiplex or next generation sequencing for broader molecular profiling to detect both common and rare driver mutations. Newer technologies, such as detection of circulating tumor cells and circulating tumor DNA, are being developed to reduce the need for invasive biopsies to obtain the genetic information required to guide targeted therapy selection.

Targeted therapy offers superior efficacy and tolerability in the treatment of advanced lung adenocarcinoma. Molecular profiling to identify a treatable mutation has become a key component of the care of these patients. It is hoped that the role of targeted therapy will continue to expand to include adjuvant treatment of early stage disease, and the ALCHEMIST trial is enrolling patients to address this question. The development of more and better drugs capable of inhibiting the diverse driver mutations found in lung adenocarcinomas is enabling more patients to benefit from this advance in cancer treatment.

Drs. Meghal and Becker are with Maimonides Cancer Center, Brooklyn, New York.

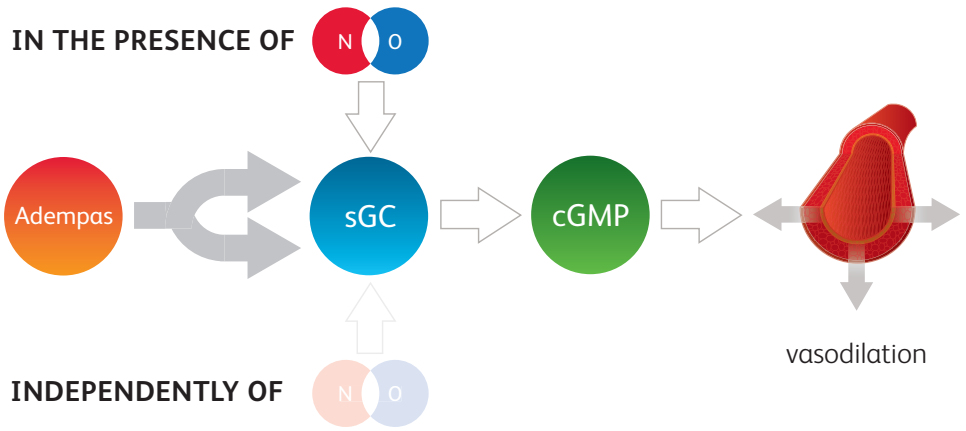


What is the role of nitric oxide (NO) in PAH and CTEPH?

- PAH and CTEPH are associated with **impaired synthesis of NO**, endothelial dysfunction, and insufficient stimulation of the NO-sGC-cGMP pathway
- **Intracellular cyclic guanosine monophosphate (cGMP)** plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation

Adempas stimulates sGC regardless of NO level to produce more cGMP

- Adempas **sensitizes** soluble guanylate cyclase (sGC) to endogenous NO by stabilizing sGC-NO binding
- Adempas directly **stimulates** sGC independently of NO via a different binding site
- Increased cGMP leads to **vasodilation**



INDICATIONS

- Adempas (riociguat) tablets are indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.*

  Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

*Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets 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, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Take your PAH and CTEPH patients farther with Adempas

FOR PAH. FOR CTEPH.

Adempas®

riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

In pulmonary arterial hypertension (PAH), (WHO Group 1)

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 443 adult PAH patients with predominantly WHO Functional Class II-III. The primary endpoint was change from baseline in 6MWD at 12 weeks.

In inoperable and persistent/recurrent chronic thromboembolic hypertension (CTEPH), (WHO Group 4)

46m improvement (mean) in 6MWD over placebo at Week 16 (95% CI: 25m-67m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 261 adult patients with persistent/recurrent CTEPH after surgery or who were inoperable. The primary endpoint was change from baseline in 6MWD at 16 weeks.

CONTRAINDICATIONS (continued)

- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients 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 Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

Bayer HealthCare LLC
100 Bayer Boulevard, Whippany, NJ 07981 USA

PP-400-US-1777 May 2015

Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

Pulmonary Veno-Occlusive Disease. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

MOST COMMON ADVERSE REACTIONS

- The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs. 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).
- Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.

Visit Adempas-US.com

BE IN THE NO

ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)**
- **For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).**

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class *[see Clinical Studies (14.1)]*.

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) *[see Clinical Studies (14.2)]*.

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program *[see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)]*.

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program *[see Warnings and Precautions (5.1)]*.

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Bleeding *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years *[See Clinical Studies (14.1, 14.2)]*.

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension *[see Contraindications (4.2) and Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension *[see Contraindications (4.3) and Clinical Pharmacology (12.2)]*. Clinical experience with co-administration of Adempas and

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat *[see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered *[see Clinical Pharmacology (12.3)]*.

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Boxed Warning and Contraindications (4.1)]*.

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas *[see Clinical Pharmacology (12.3)]*.

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus *[see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1]*.

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. 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]*.

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program *[see Warnings and Precautions (5.2)]*. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines *[see Adverse Reactions (6.1)]*. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

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Survey reveals worldwide underuse of EGFR tests

BY MITCHEL L. ZOLER
Frontline Medical News

GENEVA – Testing for mutations in the epidermal growth factor receptor gene has revolutionized treatment of advanced non–small cell lung cancer, but a significant proportion of patients with these tumors, in North America as well as elsewhere in the world, fail to undergo mutation testing at the time they are diagnosed.

Moreover, even when testing is done and a mutation is identified, a significant minority of patients do not receive treatment with a drug that can exploit their identified mutation, based on results from a recent, worldwide survey of more than 500 clinicians who manage advanced lung cancer patients.

This finding "is especially relevant given recent reports that overall survival is increased compared with chemotherapy when patients receive a specific thymidine kinase inhibitor that is matched to their mutation type," Dr. James Spicer said at the European Lung Cancer Conference.

"The reasons why many patients with cancer that contains a mutation in the EGFR [epidermal growth factor receptor] gene receive chemotherapy first line need to be understood," said Dr. Spicer, a medical oncologist at Guy's Hospital, London.

He and his associates ran the survey online during December 2014-January 2015 and received responses from 562 clinicians in 10 countries who manage patients with advanced non–small cell lung cancer (NSCLC), including 412 oncologists, 141 respiratory physicians, and 9 thoracic surgeons.

Each clinician treated, on average, 59 newly diagnosed stage-III or -IV NSCLC patients every 3 months. Responses came from 120 U.S. clinicians and 41 from Canada, who formed the North American group of respondents. Another 251 clinicians practice in Europe (France, Germany, Italy, Spain, and the U.K.), and 150 came from Asia (China, Japan, and Korea).

The Asian clinicians tested for the presence of an EGFR mutation most commonly, with 82% saying that they consistently test and await the results before starting treatment, 10% saying they routinely tested but often did not wait for the results before starting treatment, and 8% not testing.

This contrasted with 24% of the North American clinicians and 23% of those in Europe who said they did not routinely use EGFR mutation testing; 60% of the North American and 57% of the European clinicians said that they consistently test and use the results to guide their treatment decisions, Dr. Spicer reported.

Clinicians from all three continents showed a similar pattern of reasons why they did not routinely test all advanced NSCLC patients to guide treatment decisions,

Tumor histology, for example indicating squamous tissue, was the top reason, cited by two-thirds to three-quarters in the three regions, followed closely by insufficient tissue sample.

Poor performance status of patients was the third most common reason, cited by 21% in Asia, 39% in Europe, and 43% in North America.

Test results not arriving in a timely manner was a problem primarily in Europe and North America.

In Europe, 22% of responding clinicians cited delays in getting results and not wanting to wait on initiating treatment as a reason for not testing all patients. In North America, 24% of clinicians cited this reason, compared with 9% of Asian clinicians.

Perhaps most troubling was that, even when testing identifies an EGFR mutation, a significant minority of clinicians on all three continents said that they nonetheless use conventional chemotherapy first and not a thymidine kinase inhibitor.

Chemotherapy first was cited by 24% of clinicians in Europe, 19% in Asia, and 17% in North America.

In addition, 60% of the clinicians in both Europe and North America said that they do not take into account the specific EGFR mutation identified by testing when deciding on initial treatment, while 28% of Asian respondents said that this was their approach.

"These survey results provide very interesting information but need to be taken with a grain of salt," commented Dr. Tony S. Mok, the meeting's designated discussant for the report. "You need to be aware of potential biases," such as how the survey selected clinicians and the reasons why other clinicians did not respond, information not provided in Dr. Spicer's report, said Dr. Mok, professor of clinical oncology at the Chinese University of Hong Kong and Prince of Wales Hospital, Hong Kong.

Although there clearly is room for improvement in how EGFR mutation testing is performed worldwide, with the potential to improve specimen quality and cut the time needed to get testing results, the findings from this survey do not provide clear insights into the best ways to improve EGFR mutation testing in patients with newly diagnosed, advanced NSCLC, he said.

The survey was sponsored by Boehringer Ingelheim. Dr. Spicer has been an advisor to and speaker on behalf of Boehringer Ingelheim and had received research funding from the company. Dr. Mok has been a consultant to and speaker on behalf of Boehringer Ingelheim as well as several other drug companies.

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VITALS

Key clinical point: A significant minority of advanced lung cancer patients worldwide fail to receive initial treatment guided by EGFR-mutation testing.

Major finding: Among patients initially diagnosed with advanced lung cancer 17%-24% received conventional chemotherapy despite having an EGFR mutation.

Data source: Online, worldwide survey of 562 clinicians who routinely manage patients with advanced non–small cell lung cancer.

Disclosures: Survey was sponsored by Boehringer Ingelheim. Dr. Spicer has been an advisor to and speaker on behalf of Boehringer Ingelheim and had received research funding from the company. Dr. Mok has been a consultant to and speaker on behalf of Boehringer Ingelheim as well as several other drug companies.

The reasons why many patients with EGFR mutations receive chemotherapy first line need to be understood," said Dr. James Spicer.

These results provide very interesting information but need to be taken with a grain of salt, said Dr. Tony S. Mok, the designated discussant.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

New agent targets EGFR resistance in NSCLC

BY MARY ANN MOON
Frontline Medical News

A new agent targeting tumors that develop resistance to EGFR tyrosine kinase inhibitors proved to be "highly active" in a phase I trial involving 253 patients with advanced, resistant NSCLC.

Most patients who initially respond to EGFR tyrosine kinase inhibitors such as gefitinib, erlotinib, and afatinib develop resistance and show disease progression within 2 years, because the tumors develop additional EGFR mutations, particularly T790M resistance mutations. Preliminary studies suggested that a new oral agent, AZD9291, would target T790M-mediated resistance. In a phase I trial to assess its safety and efficacy, 127 study participants had known EGFR T790M mutations, and the remainder had other or unknown mutations, said Dr. Pasi A. Janne of the Lowe Center for Thoracic Oncology and the Belfer Institute for Applied Cancer Science, Dana-Farber Institute, Boston, and his associates.

The study – designed and funded by AstraZeneca, which also collected and analyzed the data in conjunction with the scientific authors – was conducted at 33 sites in Japan, South Korea, Taiwan, France, Spain, Germany, Australia, the United Kingdom, and the United States. Of the 239 patients who could be evaluated for a response, 123 (51%) showed a partial or complete response. In the subset of patients with known EGFR T790M mutations, the objective response rate was even higher, at 61%.

In contrast, the objective response rate was 21% in the subset of 61 patients who did not have known EGFR T790M mutations, the investigators said (N. Engl. J. Med. 2015 April 30 [doi:10.1056/NEJMoa1411817]).

Median progression-free survival was estimated to be 9.6 months in patients with EGFR T790M-positive tumors, although many are still alive and the final survival data have yet to be calculated. In contrast, progression-free survival was 2.8 months in patients with EGFR T790M-negative tumors.

No dose-limiting toxic effects occurred and therefore the maximal efficacy dose with an acceptable level of adverse events cannot be established yet. The most common adverse events were diarrhea (47% of patients), rash (40%), nausea (22%), and decreased appetite (21%). Serious events that were considered to be possibly treatment-related occurred in 6% of patients, and included one fatal case of pneumonia and six cases of pneumonitis-like events that resolved when the drug was discontinued.

"A structurally distinct EGFR inhibitor, one that is selective for the mutated form of EGFR, can be clinically effective and has a side-effect profile that is not dose limiting in the majority of patients in whom T790M-mediated drug resistance has developed," the researchers said.

Astra Zeneca is the maker of AZD9291. Dr. Janne reported ties to AstraZeneca, Boehringer Ingelheim, Chugai, Pfizer, Merrimack, Clovis Oncology, Roche, and Gatekeeper, as well as several patents related to genetically targeted cancer treatments; his associates reported ties to numerous industry sources.

VIEW ON THE NEWS

Lab results need rapid clinical action

Finding effective and relatively safe agents to address drug resistance in NSCLC is encouraging, and there is every reason to be cautiously optimistic about lung cancer treatment. But it is almost certain that cancer cells will continue to evolve and eventually develop resistance to these agents also.

The keys to keeping up with evolving cancers are to continue performing genomic analysis of resistant lesions and to translate laboratory findings to the clinic as rapidly as possible.

Dr. Ramaswamy Govindan is with the Alvin J. Siteman Cancer Center at Washington University, St. Louis. He reported receiving consulting fees and honoraria from Pfizer, Merck, Boehringer Ingelheim, Clovis Oncology, Helsinn Healthcare, Genentech, AbbVie, and GlaxoSmithKline. Dr. Govindan made these remarks in an editorial accompanying Dr. Janne's report (N. Engl. J. Med. 2015 April 30 [doi:10.1056/NEJMe1500181]).

CPAP by helmet better than face mask in children

BY TARA HAELLE
Frontline Medical News

VITALS

Key clinical point: Helmet CPAP is superior to facial mask CPAP for acute respiratory failure in children.

Major finding: Seventeen percent of helmet CPAP patients and 54% of face mask CPAP patients experienced treatment failure, mainly because of intolerance.

Data source: A multicenter, randomized, controlled trial involving 30 infants receiving CPAP either by helmet or face mask for RSV-induced acute respiratory failure.

Disclosures: The study did not receive external funding, and the authors reported no disclosures.

Administering continuous positive airway pressure to children for acute respiratory failure with a helmet leads to lower treatment failure rates and fewer air leaks and skin sores than does using a face mask, a recent study found.

"These results suggest that helmet CPAP was better tolerated than facial mask CPAP, with less need for sedation," reported Dr. Giovanna Chidini of Ospedale Maggiore Policlinico, Milan, and her associates.

Helmet CPAP was better tolerated than facial mask CPAP, with less need for sedation.

"Its application in mild pediatric acute respiratory failure is feasible and free from adverse events, thus allowing longer treatment than with the mask" (Pediatrics 2015 March 16 [doi: 10.1542/peds.2014-1142]).

The authors randomly assigned 30 infants, all experiencing mild acute respiratory failure resulting from respiratory syncytial virus (RSV), to receive CPAP from a helmet or from a face mask.

Treatment failure occurred in 17% (3 of 17 infants) of those using the helmet CPAP but in 54% (7 of 13) of those receiving CPAP with a face mask, primarily because of intolerance ($P = .009$).

Infants who did not tolerate the face mask did successfully tolerate the helmet after being switched.

All the infants receiving face mask CPAP required sedation, compared with 35% of those receiving helmet CPAP ($P = .02$), and more air leaks and skin sores occurred in the face mask group, despite use of protective pads.

Gas exchange and breathing patterns improved equally with both CPAP methods, but all infants required intubation within the first 24 hours because of worsening gas exchange.

No major adverse events, including cardiac arrest, pneumothorax, or safety system failures, occurred in either group.

Number of days on CPAP and the CPAP application time in the first 24 hours were similar across both groups. Length of stay in the pediatric intensive care unit did not significantly differ between the two groups, and no gastric distension, eye irritation, or mortality occurred in either group.

"The pediatric helmet was introduced in clinical practice to increase the infant's comfort while on CPAP," Dr. Chidini and her associates wrote. "The helmet is supposed to have several advantages over nasal or whole-face masks: it allows free movement of the infant's head as well as a good interaction with the environment while maintaining a good seal without compression," they said.

No standardized measure of comfort has yet been established, however, the researchers added..

EDITOR'S COMMENT

Dr. Susan L. Millard, FCCP, comments: This is an interesting concept and I would love to see a larger study address this issue.

Swallow test may raise respiratory infection risk

BY DEEPAK CHITNIS
Frontline Medical News

SAN DIEGO – There is no clear clinical benefit to diagnosing and treating infants who have abnormal swallowing, according to the results of a video fluoroscopic swallow study (VFSS).

Furthermore, in certain cases, the study could be associated with an increased risk of developing acute respiratory infections (ARI) in these populations.

In a retrospective cohort study, Dr. Eric R. Coon of the University of Utah, Salt Lake City, and his colleagues examined data on all infants aged 12 months or younger who underwent VFSS from 2010 to 2012 at Primary Children's Hospital in Salt Lake City.

"Providers implicitly believe that infant swallowing abnormalities lead to future respiratory illness," Dr. Coon said at the annual meeting of the Pediatric Academic Societies.

"However, data for that link is limited to descriptive case series, and studies relying on subjective definitions of aspiration that don't include radiographic confirmation [and] interventions for swallowing abnormalities have not been shown to improve important clinical outcomes," he added.

The investigators looked at all inpatient, outpatient, and emergency department ARI cases in the Intermountain Healthcare system, a network of 22 hospital centers servicing five states, over the same time period in patients who experienced ARI between their first VFSS and age 3 years.

ARI was defined as either bronchiolitis, asthma, pneumonia, or aspiration pneumonia, and was identified via IDC-9 codes.

Out of 576 infants, 199 (34%) exhibited oropharyngeal aspiration, 79 (14%) showed penetration, and 298 (52%)were classified as "normal." Of the 199 with aspiration, 38 (19%) had thin aspiration and cough, 11 (6%) had thick aspiration and cough, 93 (47%) had thin aspiration and were silent, and 57 (28%) had thick aspiration and were silent.

Those deemed "thick aspiration, silent," however, averaged 581 days to ARI, the shortest of any cohort, and a mean of 2.39 ARIs per subject.

"Thin aspiration, cough" subjects had 638 mean days to ARI and a mean of 1.63 ARIs; "thick aspiration, cough" subjects had a mean of 750 days to ARI and 0.55 mean number of ARIs; and "thin aspiration, silent" had an average of 669 days to ARI and a mean of 1.69 ARIs ($P < .05$).

Those in the normal, or control, cohort averaged 715 days to ARI and 1.36 ARIs, while those with just penetration averaged 681 days to ARIs and 1.53 ARIs per subject ($P < .05$).

Cox regression models were used to calculate data time to first ARI, and Poisson regression was used for data on total number of ARIs experienced.

Taking into account subject's age at initial test, presence of complex chronic conditions in each subject, result of VFSS and type of aspiration intervention, silent aspiration with thickened feed yielded a Cox hazard ratio of 1.30 and a Poisson hazard ratio of 1.47, higher than all the others.

"The clinical importance of [VFSS]-detected abnormalities remains unclear, making them high-risk for overdiagnosis," concluded Dr. Coon.

"Patients may not experience net benefit, but may in fact be harmed," he concluded.

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VITALS

Key clinical point: Infants with swallowing abnormalities who are tested with video fluoroscopic swallow study are not at any less of a risk to develop an acute respiratory infection, and at least one type of swallowing abnormality poses an increased risk for an ARI.

Major finding: Thirty-four percent of infants demonstrated oropharyngeal aspiration; silent aspiration of thick feeds had the lowest mean days to ARI (581) and highest mean number of ARIs (2.39).

Data source: Retrospective cohort study of 576 infants (age <12 months) during 2010-2012.

Disclosures: Dr. Coon did not report any relevant disclosures.

NAMDRC REPORT

Physician and patient groups weigh in on outdated CMS policy

BY DR. TIMOTHY MORRIS, FCCP
NAMDRC President
PHIL PORTE
NAMDRC Executive Director

NAMDRC, CHEST, and nine other pulmonary societies and patient groups joined together to submit a formal request to the Centers for Medicare & Medicaid Services (CMS) to rescind a key portion of a 2001 Decision Memo that requires establishment of an artificial airway when home mechanical ventilation is medically indicated.

The 2001 Decision Memo states that noninvasive mechanical ventilation "is distinguished from the invasive ventilation administered via a securely intubated airway, in a patient for whom interruption or failure of respiratory support leads to death." There are notable problems with that statement today, especially when advances in noninvasive mechanical ventilation, both in the hospital, as well as in other settings such as the home, have made NIV the standard of care for certain patients.

Also, the Durable Medical Equipment Medicare Administrative Contractors (DME MACs) continue to reference the 2001 Decision Memo as justification for recent revisions to their respiratory assist device (RAD) policies. The multisociety

The policy states noninvasive mechanical ventilation "is distinguished from invasive ventilation administered via a securely intubated airway, in a patient for whom interruption or failure of respiratory support leads to death."

request focuses not only on the need to remove the concept of an artificial airway as a requirement for home mechanical ventilation but also makes detailed recommendations for CMS to consider.

1. The request defines a mechanical ventilator as a device capable of delivering pressurized gas (either through a secured artificial airway or through a mask or mouthpiece) in a manner that repeatedly supplies a physiological tidal volume to the lungs sufficient to improve or fully sustain respiration.


DR. MORRIS


MR. PORTE

2. Mechanical ventilation is defined as the use of a mechanical ventilator on a patient in whom interruption or failure of this device can reasonably be expected to lead to eventual or rapid clinical deterioration leading to medical harm or even death.

NOTE: This emphasis is particularly important as CMS continues to ignore FDA classifications for certain devices, creating its own nebulous category of devices known as "respiratory assist devices." There is no reference in the clinical literature to these devices prior to the unilateral move by HCFA/CMS to create these classifications, ostensibly to circumvent current Medicare law that stipulates that certain ventilators must be paid under a "frequent and substantial servicing" payment methodology. By claiming the devices are not ventilators as FDA indicates but actually respiratory assist devices, the agency avoids meeting statutory payment requirements.

The request also recommends three distinct categories for CMS to consider in a revamped Decision Memo that would create three classes for payment purposes:

- use 16-plus hours per day;
- use of a mechanical ventilator greater than nocturnally alone or approximately greater than 8 hours, but less than 16 hours per day;
- and use of a mechanical ventilator (RAD) just nocturnally or up to 8 hours per day.

Detailed clinical parameters are also recommended in addition to actual usage time.

The experts from various societies that crafted this recommendation recognized that such an approach is not optimal but would represent a dramatic improvement on current CMS policies for RADs and home mechanical ventilators. The request concludes with the following statement:

Adopting the clinical parameters suggested, in tandem with documented actual usage, would add clarity to a modified Decision Memo. Furthermore, if adopted, these suggestions should enable appropriate use of more sophisticated frequent and substantially serviced equipment to recipients who stand to benefit from it and not arbitrarily denying it to the noninvasively ventilated group who are clearly in just as much need for more sophisticated equipment as the invasively ventilated patients. Therefore, a Decision Memo change that clarifies for the DME MAC contractors that reasonable criteria to afford access to the two less intensive categories noted above would ensure that less ill patients have access to more appropriate, less expensive, more easily portable devices, and their providers will not be forced to seek alternative pathways due to the regulatory barriers, as has been the case recently.

The request also recommends three distinct categores for CMS to consider in a revamped Decision Memo that would create three classes for payment purposes.

CMS has several options to consider. On some occasions, CMS simply repeals outdated policies, the effect of which is to leave policy decisions and clarifications to its contractors.

Alternatively, CMS could choose to update the 2001 Decision Memo to reflect current standards of care. Or, although unlikely, it could choose to stand by the 2001 Decision Memo and demand that an artificial airway be present for beneficiaries who need home mechanical ventilation.

President's Report: Collaboration across CHEST

BY DR. CURTIS N. SESSLER, FCCP
President, CHEST

Now that I am at the midway point in my presidential term, I would like to share good news about recent activities that are the result of exceptional collaboration.

This month marked a major milestone, as CHEST launched a robust, new association management software (AMS) system to improve and simplify the way that members engage with us online. Go-live has gone smoothly, and the CHEST staff is quickly addressing the minor issues members and customers have encountered. Congratulations to the entire CHEST staff on a successful launch.

The Innovation, Simulation, and Training Center in Glenview continues to be an important center of activity. So far, we have attracted more registered participants to this year's courses than we had in FY13-14, and participation is expected to top 900 learners. Ultrasound courses continue to attract the largest attendance, but newer simulation courses, like the Comprehensive Pleural Procedures course in June and Difficult Airways course in August, are expanding our offerings for the busy clinician.

CHEST continues to collaborate with the Chinese Thoracic Society on several fronts. In April, Dr. Darcy Marciniuk and colleagues traveled to China to continue CHEST's work on collaborative development of a PCCM specialty for Chinese physicians. In July, we'll be back in China offering a "Best of CHEST" program in Beijing, and we'll also be meeting with Chinese program committee representatives for CHEST World Congress (CWC) 2016. Registration for the April 2016 meeting will open before the Chinese Thoracic Society meeting in September.

The CHEST Foundation is having an outstanding year, as well. New efforts include the "I'm in the Family" campaign, a new Donor Spotlight newsletter, and the launch of patient-focused public education tied to disease awareness months. This new program, which is the fastest growing in the foundation, will account for one-third of the CHEST Foundation's income this year, while increasing visibility—including presence during Green Bay Packers' games, the Daytona 500, and at the Indy 500. CHEST and the foundation also will lead the way with promotional efforts in lung cancer awareness by helping sponsor "World Lung Cancer Day" this year on August 1.


DR. SESSLER

On the membership front, CHEST continues to retain more than 90% of its members year-to-year, while introducing a new membership model this month that expands membership to students, interns, and residents, as well as to the broader interdisciplinary team of chest medicine professionals. We want to continue to be a welcoming home for our chest medicine trainees – fellows, and as of April 30 this year, 1,757 fellows (92% of all US chest medicine fellows) – are members of CHEST. By creating new opportunities for students and allied health professionals to become engaged in CHEST, and opening FCCP eligibility to distinguished professionals beyond physicians and PhDs , we expect membership and leadership participation will grow, as well.

More than 100 leaders from CHEST committees and the Board of Regents visited CHEST Global Headquarters for meetings in April, where some significant progress on a number of fronts was made. Highlights include the following:

- The Board of Regents approved an update to CHEST bylaws, opening Fellowship to all healthcare professionals who meet updated FCCP qualifications.
- Key stakeholders contributed to discussions around updating our strategic plan and organizational goals, ensuring that the essential work done by our volunteer groups continues to align with the direction of the organization.
- Committee, board, and staff leaders participated in conflict resolution training.
- *CHEST* journal staff held an all-day meeting with Elsevier staff in an effort to start mapping editorial and production workflows for the upcoming transition to Elsevier being our journal publisher in 2016.

Continued on page 50

CHEST 2015: Quintessential Montréal, one-of-a-kind meeting

There's nothing more Canadian than hockey, and nothing as "quintessential Montréal" as Mount Royal, the namesake of the city. When CHEST travels to Montréal for the CHEST Annual Meeting 2015, October 24 to 28, you'll have the opportunity to make the most of your visit. In your free time, you can explore all of the classic and eclectic Montréal activities.

First up: Mount Royal. Mount Royal Park has status similar to New York's Central Park. This mountain, located immediately west of downtown, is nicknamed the "lungs of Montréal." It's fitting that every chest medicine professional should visit this city landmark and enjoy breathtaking views of the city skyline and year-round activities.

After you get your exercise at Mount Royal, you may be looking to sit back, relax, and be entertained. Take in a show at Place des Arts located in the heart of the Quartier des spectacles on Saint Catherine Street. This cultural complex is made up of six performance halls and has 8,000 seats for spectators to enjoy theater, opera, dance, musicals, concerts, and much more.

If music and theater aren't your speed, perhaps you'd rather take in a hockey game at Montréal's Bell Centre. Locals are devoted to the Canadiens, the most-winning franchise in the NHL. When in Canada, live like a local and cheer for the aptly named Canadiens!

If you're looking for a more cultural experience, check out the Montréal Museum of Fine Arts. The museum acquires and promotes works by artists of yesterday and today, local and international. You'll enjoy paintings, sculptures, graphic arts, photographs, and decorative art objects displayed in four pavilions.

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And you can't return home without filling your suitcase with something you found on a shopping excursion. Montréal is a shopper's paradise with these must-see destinations:

Jean-Talon Market: Located in the heart of Little Italy, this farmer's market serves up fresh food to crowds year-round.

Underground City: This multilevel network of tunnels and stairs connects shopping malls, metro stations, offices, schools, hotels, concert halls, and more.

Saint Catherine Street: Find many of Montréal's prominent retailers on this primary street in downtown Montréal.

Saint Denis Street: This trendy, upscale street is home to lots of shops and restaurants and is a major thoroughfare in downtown Montréal.

Montréal will keep you entertained with its distinct charm and many activities. CHEST 2015 will keep you busy with many different learning formats and sessions. You'll receive an insightful education and a one-of-a-kind experience.

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In Memoriam

Past President (1980-1981) of the American College of Chest Physicians, Dr. John (Jack) G. Weg, Master FCCP, died on May 3, 2015. Jack had a distinguished career of more than 40 years at the University of Michigan in Ann Arbor, where he continued to serve as Professor Emeritus of Internal Medicine in the Division of Pulmonary and Critical Care Medicine at the time of his passing. Jack's involvement with CHEST similarly spanned almost 40 years and included not only his term as President and being honored as a Master Fellow but also serving as chair of numerous committees and courses, and being a long-time member of the *CHEST* Editorial Board. In a recent video interview slated for *CHEST*'s Giants in Chest Medicine series, Jack cited one of his greatest education accomplishments as his involvement with the creation and introduction of ACCP-SEEK. He was the *CHEST* Department Editor for "ACCP-SEEK Board Review Question of the Month" for 10 years. Jack prided himself on encouraging young physicians to get involved with CHEST, and he worked with the organization through the years to continually enhance the quality of the education the organization provided for physicians, nurses, and other medical professionals. All who had the pleasure of knowing Jack will miss him and will remember the important role he played in helping establish modern clinical pulmonary medicine. We extend heartfelt condolences to the Weg family.

DR. WEG

This month in *CHEST*: Editor's Picks

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

Supplementing Defect in Club Cell Secretory Protein Attenuates Airway Inflammation in COPD. *By Dr. A. Gamez et al.*

A Pilot Study of the Noninvasive Assessment of the Lung Microbiota as a Potential Tool for the Early Diagnosis of Ventilator-Associated Pneumonia. *By Dr. A. K. May et al.*

Short Telomeres, Telomeropathy, and Subclinical Extrapulmonary Organ Damage in Patients With Interstitial Lung Disease. *By Dr. G. George et al.*

COMMENTARY – AHEAD OF THE CURVE
Ethical and Practical Considerations in Providing Critical Care to Patients With Ebola Virus Disease. *By Dr. P Torabi-Parizi et al.*

RECENT ADVANCES IN CHEST MEDICINE
BLUE-Protocol and FALLS-Protocol: Two Applications of Lung Ultrasound in the Critically Ill. *By Dr. D. A. Lichtenstein.*

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE
Mechanical Ventilation for Severe Asthma. *By Dr. J. Leatherman.*

CONTEMPORARY REVIEWS IN SLEEP MEDICINE
Surgical Management of OSA in Adults. *By Dr. D. F. Smith et al.*

TOPICS IN PRACTICE MANAGEMENT
Clinical and Billing Review of Extracorporeal Membrane Oxygenation. *By Dr. J. M. Blum et al.*

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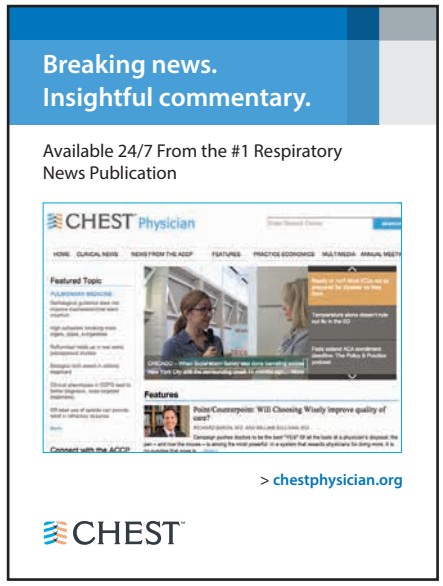

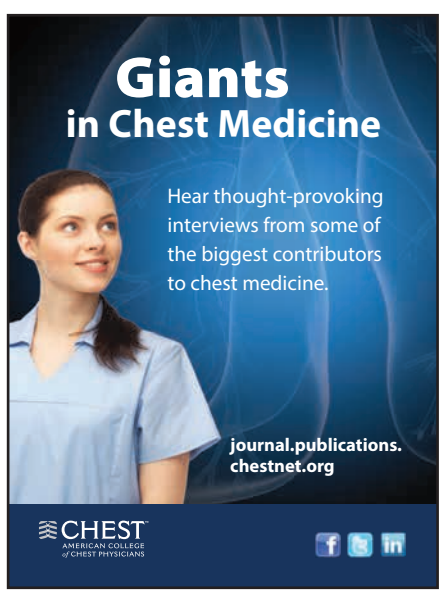

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FCCP designation opened more broadly

The Fellow of the American College of Chest Physicians (FCCP) designation has been expanded to a broader audience of chest medicine professionals to align with CHEST's focus on engaging the entire chest medicine team. FCCP requirements also have been updated. The following new requirements are now in place:

• FCCP applicants must demonstrate excellence in one or more of the following key domains: excellence in clinical chest medicine; certifications, recognition, and awards; leadership, teaching, and patient education; publications and abstracts; and conferences.
• FCCP applicants must be CHEST members for 2 or more years at the Enhanced or Premium level of membership.
• FCCP applicants must be board-certified or hold a professional degree.

All FCCP applications are reviewed on an individual basis, based upon the requirements outlined above, or equivalent qualifications.

These changes to the FCCP designation apply to all future applicants. Current FCCPs will not be required to submit additional material to maintain the FCCP designation but must remain an active member at the Enhanced or Premium membership level. Complete requirements and application details are available at chestnet.org.

Continued from page 47

• Dr. Richard Irwin, Dr. Cindy French, and the *CHEST* journal Associate Editors held a productive strategic planning meeting with Elsevier and journal staff, identifying key areas for which Elsevier can provide data that will help in making informed decisions about the journal and its content moving forward.

• Journal staff conducted a half-day training session on the Scholar One Manuscript Central system with Dr. John Heffner, who has been appointed as the Deputy Editor of *CHEST*.

• Education Committee approved a new committee structure that better defines its role and will better serve to support our activities.

• Council of NetWorks came up with a scorecard concept for how they will track NetWorks progress and engagement going forward.

• Guidelines Oversight Committee discussed establishing a clear vision for our guidelines portfolio and tackled policy matters, such as opening guidelines up for a public comment period and seeking broader funding to support development efforts.

The leadership and collegiality I witnessed throughout all of these meetings made me proud to serve among such a committed group of chest medicine professionals. I look forward to the next half of my term, as we continue to collaborate on efforts that advance the mission and vision of CHEST.

Erratum/Clarification

In the January 2015 issue of *CHEST Physician*, on pages 22-23, the article states, "Four products are approved in the United States, which include nebulized and dry powder forms of tobramycin and colistin and nebulized aztreonam … [and] inhaled dry powder ciprofloxacin." Correction: the only FDA-approved inhaled antibiotics include tobramycin and aztreonam for CF only. Neither inhaled colistin nor ciprofloxacin is approved by the FDA for any condition. Further, the mention of "off-label" nebulized medications was not intended to "encourage" their use, which is subject to individual institutions and restrictions applied in such institutions.

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NETWORKS

Allied Health

Opening Pandora's Box: the role of anxiety and depression in asthma/COPD

Over 23 million individuals have the diagnosis of COPD with a similar number of asthma diagnoses. Psychological factors are well-known to impact the frequency and severity of exacerbations (and resultant hospitalization and missed days of work/school), quality of life, and nonadherence with medical therapy. The exact prevalence of anxiety and depression among patients with asthma/COPD is unknown but conservative estimates exceed 50%.

The connection between anxiety and emotion and airway hyperresponsiveness is not new—Hippocrates is credited as the first to believe that control of one's anger was a means of preventing an asthma attack. Centuries later, in the seminal work, *The Production of Rose Asthma by an Artificial Rose*, MacKenzie (1886) documented the development of a severe allergic reaction by a patient to an artificial rose in his office. Osler referred to asthma as a "neurotic affection," and asthma was felt to be a psychological manifestation earning the moniker "asthma nervosa."


MR. UNKLE

The relationship between psychological dysfunction and the morbidity (and the direct and indirect costs) of asthma/COPD offers another opportunity for disease management in this population. One example is the anxiolytic agent, buspirone, used successfully in patients due to respiratory stimulation and the lack of neural respiratory depression actions of other agents.

With a heightened emphasis on exacerbation reduction in both disorders, screening evaluation for psychological comorbidity may result in improvement in disease management and warrants inclusion in the future development of management guidelines for these disorders.

David W. Unkle, MSN, APN
Steering Committee Member

Chest Infections

Highly pathogenic avian influenza comes to the United States

Avian influenza is caused by influenza A viruses. Influenza A virus is classified into subtypes based on the combination of 16 different types of HA antigens (H1 to H16) with nine different NA antigens (N1 to N9). All known subtypes of influenza A can be found in birds, and wild aquatic birds are the major reservoir for influenza A viruses. Influenza virus is constantly changing its structure by a process called genetic reassortment. When a cell is co-infected with two different subtypes, a new reassortant progeny may develop with two different RNA segments from two different subtypes.

Avian influenza A virus strains are further classified as low pathogenic (LPAI) or highly pathogenic (HPAI) on the basis of specific molecular genetics and pathogenesis criteria that require specific testing. Most avian influenza A viruses are LPAI viruses that are usually associated with mild disease in poultry. In contrast, HPAI viruses can cause severe illness and high mortality in poultry.

Since 2008, reassortment of H5N1 subtype viruses have generated new HPAI H5Nx subtypes. Particularly important is the H5N5 reassortant virus, which in turn has led to the generation of a range of novel H5Nx reassortants like H5N2, H5N6, and H5N8 subtypes (Vries et el. *Emerg Infect Dis*. 2015;21[5]:842). The H5N6 reassortant became particularly concerning after spreading over a wide geographic area in Southeast Asia and causing a fatal human infection in China. The H5N8 subtype spread to Europe in November 2014, resulting in large economic losses in the poultry industry. For the first time in the history of the United States, in December 2014, HPAI (H5N8 and specifically H5N2) started being detected and have continued to date in 2015. USDA is reporting HPAI detections in 20 US states (http://www.cdc.gov/flu/avianflu/h5/index.htm).

Although no cases have been reported in the United States, human infection with HPAI (H5N1), (H5N6), and (H7N9) viruses has been reported elsewhere and was associated with severe, sometimes fatal, disease (Gao et al. *N Engl J Med*. 2013;368[24]:2277).

In the backdrop of unstoppable HPAI outbreaks in the Midwest, public health authorities as well as relevant professional bodies must prepare themselves for a possible human outbreak. In the meanwhile, the general public should be advised to avoid contact with wild birds, domestic birds, or poultry that appear ill or have died and surfaces that appear to be contaminated with feces from wild or domestic birds. The CDC has issued public health guidance for high-path AI H5 testing and preventive medication of people exposed to these viruses. People who have had contact with infected birds should monitor their own health for possible symptoms, for example, flu-like symptoms or conjunctivitis. People who have had contact with infected birds may also be given influenza antiviral drugs preventatively.

Dr. Rumi Ahmed Khan, MBBS, FCCP
Steering Committee Member

Cardiovascular Medicine and Surgery

New anticoagulation drugs for stroke prevention in AF

Since 2010, three new oral anticoagulants have received FDA approval for stroke prevention in atrial fibrillation, which is the focus of this update. Three landmark trials were reviewed:

RE-LY (Stuart et al. *N Engl J Med*. 2009;361[12]:1139; Conelly et al. *Circulation*. 2013;128[3]:237).

Compared with warfarin, dabigatran 150 mg twice-daily lowered primary outcome of stroke/systemic embolism by 34% (number needed to treat (NNT)/yr 169) and had similar incidence of major bleeding.

ROCKET-AF (Manesh et al. *N Engl J Med*. 2011;365[10]:883) Rivaroxaban demonstrated noninferiority compared with the warfarin group for the primary outcome of stroke and systemic embolism and major bleeding.

ARISTOTLE (Christopher et al. *N Engl J Med*. 2011;365[11]:981) Apixaban showed a relative risk reduction for the primary outcome of 21% (NNT 300), and lowered major bleeding down by 31% (NNT/yr 104). Apixaban also showed mortality benefit compared with warfarin (3.52 vs 3.94%/year, P .047).


DR. TSAI

All three oral anticoagulants lowered rates of intracranial hemorrhage. The use of rivaroxaban and apixaban has been projected to reduce medical costs when compared with warfarin, and dabigatran is projected to have similar costs. All three oral anticoagulants have robust RCTs supporting their comparability to warfarin therapy for stroke prevention in nonvalvular atrial fibrillation, with apixaban showing superiority in incidence of strokes, major bleeding, and mortality.

These new drugs, unlike warfarin, do not require titration and aim to improve patient management with atrial fibrillation relevant to the daily practice of cardiologists, cardiothoracic surgeons, and intensivists.

Dr. Peter I. Tsai, FCCP
Steering Committee Member
Dr. Nasser M. Lakkis, FAAC

Clinical Pulmonary Medicine

Steroids in community-acquired pneumonia

Host inflammatory response is crucial when facing CAP. Minimal or excessive cytokine response is detrimental. Steroids are the most widely used immunomodulators. The interest on using steroids for the CAP treatment has re-emerged.

Randomized controlled clinical trials have shown mixed results. One study (Mejivis et al. *Lancet*. 2011;377[9782]:2023) found similar cure rates but shorter hospital stay in CAP inpatients treated with dexamethasone for 4 days. Another study (Snidjers et al. *Am J Respir Crit Care Med*. 2010;181[9]:975) found an increased late (>72 h since admission) clinical failure rate in CAP patients treated with prednisolone for 7 days.

Severe CAP is associated with a stronger inflammatory response and worse outcomes. Steroids may offer an advantage in this specific population. The Critical Care study (Fernandez et al. *Crit Care*. 2011;15[2]:R96) showed a faster Po_2/Fio_2 and fever and radiology improvement in patients taking methylprednisolone over placebo.


DR. DANCKERS

There was a trend toward shorter ICU stay and mechanical ventilation therapy in the steroid group.

The JAMA study (Torres et al. *JAMA*. 2015;313[7]:677) noticed that severe CAP patients with elevated C-reactive protein (>150 mg/L) had faster radiologic improvement and lower septic shock rates when treated with methylprednisolone for 5 days rather than placebo.

The STEP trial (NCT00973154), recently completed, has enrolled 800 patients with CAP and treated them with prednisone or placebo for 7 days. Outcomes measured included time to clinical stability, adrenal function, inflammatory biomarkers, recurrence, and mortality rates. The ESCAPe trial (NCT01283009) is recruiting up to 1,450 veterans with severe CAP. Patients will receive methylprednisolone or placebo for 7 days with a 2-week taper, looking at 60-day all-cause mortality.

We hope that growing evidence will further clarify the role of steroids in CAP.

Dr. Mauricio Danckers
Steering Committee Member

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