

# Vasoreactivity Testing a Must in Idiopathic PAH

Oral calcium channel blockers have no place in this testing, warns an ACC/AHA consensus statement.

BY BRUCE JANCIN

SAN DIEGO — Only 1 in 20 individuals with idiopathic pulmonary arterial hypertension can be successfully managed long term with oral calcium channel blockers, but even a slim chance of using this simple, inexpensive therapy is so attractive that acute vasoreactivity testing to identify suitable candidates is warranted in all patients with the disorder.

The best agent to use for this testing, which is done during right heart catheterization, is inhaled nitric oxide, Dr. Lewis J. Rubin said at the annual meeting of the American College of Chest Physicians.

"It's very potent, it's short acting, it's a very good identifier of patients who have vasoreactivity—and when you see it, there's no question about it. Within a few breaths of nitric oxide in a responder, you will see the pulmonary artery pressure come down. It's not subtle at all," said Dr. Rubin, professor of pulmonary and critical care medicine at the University of California, San Diego.

Roughly 10% of patients with idio-

pathic pulmonary arterial hypertension (IPAH) will demonstrate a dominant vasoreactive response on testing and therefore are suitable for a therapeutic trial using an oral calcium channel blocker. Earlier studies had put that figure as



**IPAH is a highly complex, rapidly evolving condition to manage. 'We serve as a resource for you.'**

DR. RUBIN

high as 20%-25%.

Alternatives to inhaled nitric oxide for acute vasoreactivity testing are intravenous epoprostenol (Flolan) and intravenous adenosine.

Calcium channel blockers should never be used for the testing, a point that was emphasized in the latest American College of Cardiology/American Heart Association expert consensus document on pulmonary hypertension, coauthored

by Dr. Rubin (J. Am. Coll. Cardiol. 2009;53:1573-619).

"They're nontitratable and nonselective, and it's exceedingly dangerous. So you either test for vasoreactivity with something that's available and safe, or you don't do it and you let somebody who does this for a living do it for you," Dr. Rubin said.

Only a tiny percentage of patients with PAH that is associated with connective tissue disease, portal hypertension, HIV infection, or other nonidiopathic forms of PAH have pulmonary vasoconstriction as the dominant cause of their pulmonary hypertension and are thus candidates for calcium channel blocker therapy.

"Some people say there's no use in testing for acute vasoreactivity in anything other than IPAH. But if you're set up to do it and you can do it relatively efficiently, safely, and quickly, I think it's worth doing for all patients with PAH," the physician continued.

Dr. Rubin made a plea for physicians in the community to have no hesitation in referring their patients with PAH to experts at centers of excellence. "This is a highly complex and rapidly evolving condition in terms of management. As treatments have diffused into the com-

munity, I think there are concerns about delays in referring patients for more complex management. This is a shared responsibility. We can't see these patients as frequently as you can because they often come from a distance. We serve as a resource for you. We need to see these patients at intervals," he said. ■

**Disclosures:** Dr. Rubin disclosed that he is a consultant and/or on the speakers bureaus for Gilead Sciences Inc., Actelion Pharmaceuticals Ltd., Pfizer Inc., United Therapeutics Corp., Aires Pharmaceuticals Inc., Solvay Pharmaceuticals Inc., and other pharmaceutical companies.

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## ACTEMRA® (tocilizumab)

In the all-exposure population, the rate of malignancies remained consistent (1.10 events per 100 patient-years) with the rate observed in the 6-month controlled period [see Warnings and Precautions].

### Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 mg/kg or 8 mg/kg ACTEMRA plus DMARD, and at least 1% greater than that observed in patients on placebo plus DMARD, are summarized in Table 2.

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 mg/kg or 8 mg/kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

	6-Month Phase III Controlled Study Population				
	ACTEMRA 8 mg/kg Monotherapy	Methotrexate	ACTEMRA 4 mg/kg + DMARDs	ACTEMRA 8 mg/kg + DMARDs	Placebo + DMARDs
Preferred Term	N = 288 (%)	N = 284 (%)	N = 774 (%)	N = 1582 (%)	N = 1170 (%)
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

### DRUG INTERACTIONS

#### Other Drugs for Treatment of Rheumatoid Arthritis

Population pharmacokinetic analyses did not detect any effect of methotrexate, nonsteroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance.

Concomitant administration of a single dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists [see Dosage and Administration].

#### Interactions with CYP450 Substrates

In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, eg, oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

#### Live Vaccines

Live vaccines should not be given concurrently with ACTEMRA [see Warnings and Precautions].

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

**Teratogenic Effects. Pregnancy Category C.** There are no adequate and well-controlled studies in pregnant women. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg/kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphic effect at any dose, tocilizumab produced an increase in the incidence of

## ACTEMRA® (tocilizumab)

abortion/embryo-fetal death at 10 mg/kg and 50 mg/kg doses (1.25 and 6.25 times the human dose of 8 mg/kg every 4 weeks based on a mg/kg comparison).

### Nonteratogenic Effects

Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

### Pregnancy Registry:

To monitor the outcomes of pregnant women exposed to ACTEMRA, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

### Nursing Mothers

It is not known whether tocilizumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

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

### Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. The frequency of serious infection among subjects treated with ACTEMRA 65 years of age and older was higher than those under the age of 65. As there is a higher incidence in infections in the elderly population in general, caution should be used when treating the elderly.

### Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology [see Warnings and Precautions].

### Renal Impairment

No dose adjustment is required in patients with mild renal impairment. ACTEMRA has not been studied in patients with moderate to severe renal impairment.

### OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported in which a patient with multiple myeloma received a dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg/kg, although all 5 patients at the highest dose of 28 mg/kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

### PATIENT COUNSELING INFORMATION

#### Patient Counseling

Patients should be advised of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

#### • Infections:

Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

#### • Gastrointestinal Perforation:

Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

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