Psoriatic Arthritis Criteria Help Assess Tx Benefits

**By Sara Freeman**

From the Annual Meeting of the British Society for Rheumatology

**Birmingham, England —** Radiologic damage is reduced in patients with psoriatic arthritis that is treated with anti-tumor necrosis factor if they meet new minimal disease activity criteria, according to Dr. Laura C. Coates. This first, and only, composite measure developed for psoriatic arthritis could potentially be used as an objective target or outcome measure in clinical tri- als, Dr. Coates said at the meeting.

“Minimal disease activity is a concept that has been defined by the Outcome Measures in Rheumatology Arthritis Clinical Trials group as a state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations,” explained Dr. Coates of the University of Leeds (England).

Dr. Coates and her associates have recently developed minimal disease activity (MDA) criteria for psoriatic arthritis using data on 40 patients with the disease and the expert opinions of rheumatologists and dermatologists (Ann. Rheum. Dis. 2010;69:48-53).

For a patient to meet MDA, five of the following seven criteria must be met:
- A tender joint count less than or equal to one.
- A swollen joint count less than or equal to one.
- A Psoriasis Area and Severity Index score less than or equal to 1 or a body surface area less than or equal to 3.
- A patient pain visual analog score (VAS) less than or equal to 15.
- A patient global activity VAS less than or equal to 20.

**REVATIO® (SILDENAFIL)**

_Brief Summary of Prescribing Information_**

**INDICATIONS AND USAGE:** REVATIO® is indicated for the treatment of pulmonary arterial hypertension (PAH; Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO® was added to background vasodilator therapy.

**Limitation of Use**

The efficacy of REVATIO has not been adequately evaluated in patients taking beta-blockers concurrently.

**DOSE AND ADMINISTRATION**

**Pulmonary Arterial Hypertension (PAH)**

**REVATIO Tablets**

The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food.

In the clinical trial, no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

**REVATIO injection**

REVATIO injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication.

The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight.

A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

**CONTRAINDICATIONS**

Use with Organic Nitrates

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/GMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

**Hypersensitivity Reactions**

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet.

Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reaction/shock events and anaphylactoid reactions. The majority of reported events were non-serious hypersensitivity reactions.

**WARNINGS AND PRECAUTIONS**

_Cardiovascular Effects_**

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients with resting hypotension [BP < 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction).

Pulmonary vasodilators may worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur during administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO should be stopped.

**INTERACTIONS**

Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, resulting in symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and syncope were reported (see Drug Interactions).

Co-administration of sildenafil and its N-desmethyl metabolite was associated with an increased risk for the combined composite primary efficacy endpoint in the endothelin antagonists clinical trials (one of two pivotal trials). A pooled analysis of the four randomized controlled clinical trials included in the primary endpoint analysis showed an increase in the risk of symptomatic hypotension (systolic blood pressure < 90 mm Hg and diastolic blood pressure < 50 mm Hg) with sildenafil, especially in patients taking concomitant alpha-blockers, compared to placebo. Hence, sildenafil should be used with caution in these patients.

**EFFECTS ON BLEEDING**

In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on inhibition of thrombin-induced platelet aggregation in vitro.

The incidence of epistaxis was 3% in patients taking sildenafil with PAH secondary to connective tissue disease (CTD). This effect was not seen in primary pulmonary hypertension (PPH) (sildenafil 3%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-treated patients with a concomitant oral vitamin K antagonist (9% versus 2%) in those not treated with concomitant vitamin K antagonists.

The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Use with Rituximab and Other Potent CYTOX® Inhibitors

The co-administration of the protease inhibitor rituximab (a highly potent CYTOX® inhibitor) substantially increases serum concentrations of sildenafil. Therefore, co-administration of rituximab or other potent CYTOX® inhibitors with REVATIO is not recommended.

**Clinical Trials Experience**

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

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dosage of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled, open pulmonary arterial hypertension trials, the adverse drug reactions that were reported by at least 3% of REVATIO-treated patients at the recommended dosage (20 mg TID) were headache, hypertension (BP > 170/110), and alanine aminotransferase (ALT) elevations compared to placebo patients as shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

**Table 1.** REVATIO All Causality Adverse Events in ≥3% of Patients and More Frequent (≥1%) than Placebo

<table>
<thead>
<tr>
<th>ADEVERSE EVENTS</th>
<th>PLACEBO (%)</th>
<th>REVATIO 20 mg TID (%)</th>
<th>PLACEBO-Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>48</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Blushing</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Priapism</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dysthchia</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

The safety and efficacy of combinations of REVATIO with WARPA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VGRA or other PDE5 inhibitors.

**Prolonged Erection**

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

**ADVERSE REACTIONS**

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

- **Hypotension** (see Warnings and Precautions)
- **Vision loss** (see Warnings and Precautions)
- **Hearing loss** (see Warnings and Precautions)
- **Priapism** (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 compared directly to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared directly to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an add-on to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (>5% difference) are shown in Table 2.

### Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (>4%) than Placebo

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo Epoprostenol (n = 131)</th>
<th>REVATIO Epoprostenol (n = 134)</th>
<th>Placebo-Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34</td>
<td>57</td>
<td>23</td>
</tr>
<tr>
<td>Edema[^a]</td>
<td>14</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>18</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

[^a]includes peripheral edema

### Cardiovascular Events

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

### Decreases in and Loss of Vision

When used that erectile dysfunction, non-arteric anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported. In drug-drug interaction studies, sildenafil (4 mg or 8 mg) or alprostadil administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on alpha-blockers in two studies, mean additional reductions of supine systolic and diastolic blood pressure of 7/6 mmHg, 8/5 mmHg, and 4/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/4 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light headedness, but not syncope.

### Amiodipine

When sildenafil 100 mg was co-administered with amiodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 6/5 mmHg and 7/6 mmHg diastolic.

### USE IN SPECIFIC POPULATIONS

**Pregnancy**

Pregnancy Category B

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 60-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a study in rabbits at a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its metabolites similar to those seen at lower doses but rates and severities were increased.

### Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery has not been studied.

### Nursing Mothers

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

### Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

### Geriatric Use

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

### Hepatic Impairment

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

### Renal Impairment

No dose adjustment is required (including severe impairment Clcr < 30 ml/min).

### OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

### In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

### NONCLINICAL TOXICOLOGY

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats at doses up to 80 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 37 times, for male and female rats respectively, the human exposure at the RHD of 20 mg TID. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m² basis.

Sildenafil was negative in in vitro bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and in vivo lymphohematopoietic and in vivo mouse micronucleus assay to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 39 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

### PATIENT COUNSELING INFORMATION

#### • Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

#### • Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction.

#### • Advise patients to seek prompt medical attention in the event of a sudden decrease or loss of vision while taking REVATIO. These events may be accompanied by lid thickness and light headedness.

### DRUG INTERACTIONS

#### Nitrates

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

#### Alcohol and Other PDE5 Inhibitors

Concomitant use of REVATIO with ritanserin and other PDE5 inhibitor (CYP3A inhibitors is not recommended (see Warnings and Precautions).

#### Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects (see Warnings and Precautions).

### THE x-ray shows distal phalangeal joint damage from psoriatic arthritis.

Patients achieved MDA after 24 weeks of study (P = .001). At 1 year, when all patients were receiving infliximab, 40% of patients were in MDA. Again, comparing the patients who were in MDA at week 52 with those who were not showed that 78% and 57% showed no signs of radiologic progression (P = .009).

Around 40%-50% of patients with psoriatic arthritis can achieve MDA with anti-TNF therapy, Dr. Coates said. She noted that the placebo response was low and that patients who achieve MDA “are more likely to halt their radiographic progression.”

A limitation of the study was that little radiographic progression occurred in the cohort of patients studied.

“This is the only composite disease activity measure that has been developed for psoriatic arthritis to date,” Dr. Coates said. “It encompasses measures of joint disease, skin disease, entheses, and patient-reported outcomes, so it really does cover a wide variety of psoriatic disease.”

One of the advantages of using the measure, Dr. Coates noted, is that it can be used “cross-sectionally” and on any day to determine whether MDA is achieved. Furthermore, it confirms a satisfactory level of disease activity, not just a response to treatment, as the current American College of Rheumatology or Psoriatic Arthritis Response Criteria do.