

Methotrexate-Related GI Upset Common in JIA

BY BRUCE JANCIN

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

ROME — Methotrexate-induced gastrointestinal side effects in juvenile idiopathic arthritis patients are extremely common—and even more so with par-enteral than with oral therapy, suggesting the nausea has a psychological basis that might be amenable to cognitive-be-

havioral therapy, according to findings of a Dutch study.

“This was a surprise. In daily practice, many doctors say that if you’re intolerant to an oral medication and there’s a subcutaneous alternative, you switch to subcutaneous, of course. And we did. And we found the methotrexate intolerance score was higher in the subcutaneous than [in] the oral group,” Dr. Nico M. Wulfraat said. Methotrexate intolerance

was unrelated to the drug dose, disease activity or duration, JIA subtype, or treatment duration. The only predictor in this study was the route of administration.

Hepatotoxicity and hematologic abnormalities are the methotrexate side effects most physicians are preoccupied with, even though they occur in only a minority of pediatric patients and are often mild and transient.

In contrast, GI side effects (chiefly nau-

sea and vomiting) were a significant problem for 55% of the 283 JIA patients in the study. The rate was 50% among those on oral therapy and 69% in youths on injectable methotrexate, reported Dr. Wulfraat, a pediatric rheumatologist at Wilhelmina Children’s Hospital in Utrecht, the Netherlands.

“This is very clinically relevant. In a large proportion of patients these side effects end in early discontinuation of oth-

REVATIO® (SILDENAFIL)

Brief Summary of Prescribing Information

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

Limitation of Use

The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

DOSAGE 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 bolus 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/cGMP 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 reaction. 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 significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

As there are no controlled clinical data on the safety or efficacy of REVATIO in the following groups, prescribe with caution for:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP > 170/110);
- Patients currently on bosentan therapy.

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, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported [see Drug Interactions]. No cases of syncope or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

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 bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The incidence of epistaxis was 13% 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 antagonist).

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

Use with Ritonavir and Other Potent CYP3A Inhibitors

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A inhibitor) substantially increases serum concentrations of sildenafil; therefore, co-administration of ritonavir or other potent CYP3A inhibitors with REVATIO is not recommended.

Effects on the Eye

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE5 inhibitors, including REVATIO. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors [see Adverse Reactions].

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

Hearing Impairment

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [see Adverse Reactions].

Combination with other PDE5 inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

Prolonged Erection

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

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 directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data were obtained from the 12 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied.

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

In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are 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

ADVERSE EVENTS %	Placebo (n=70)	Revatio 20 mg TID (n=69)	Placebo-Subtracted
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis nos	0	4	4
Diarrhea nos	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis nos	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

nos: Not otherwise specified

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

The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

erwise effective therapy," he observed. "There is a lot of refusal to take the medication among our small children. And many schoolchildren say their weekends are ruined. That's because most boys and girls take the drug on Fridays, knowing they're going to feel bad for several days, and they don't want it to affect school."

These pervasive GI symptoms in JIA patients are best viewed as a psychological side effect of methotrexate. Anticipatory nausea and anxiety figure prominently in the clinical picture. And the fact that the symptoms occur so frequently with parenteral therapy argues

against direct mucosal toxicity as the mechanism.



These side effects can end in an early discontinuation of otherwise effective therapy.

DR. WULFFRAAT

Asked if early introduction of antiemetic agents in conjunction with

methotrexate helps curb the GI side effects, Dr. Wulfraat explained that although pediatric oncologists routinely use this strategy when prescribing nausea-inducing chemotherapeutic agents, he hasn't found it effective in the setting of methotrexate for JIA.

However, based on a favorable pilot study he and his coworkers conducted (Clin. Exp. Rheumatol. 2007;25:480-5), Dr. Wulfraat and coinvestigators have launched an ongoing, large, multicenter, randomized clinical trial in which Dutch and German methotrexate-treated JIA patients with anticipatory nausea are be-

ing randomized to one of three study arms: continuation on methotrexate as before, switching the route of administration, or continuing the medication while receiving cognitive-behavioral therapy. The goal is to establish whether psychotherapy can help patients with JIA stay on this effective, cheap, and safe drug. ■

Disclosures: The study is funded by the Dutch League Against Rheumatism and Medac, a German manufacturer of methotrexate. Dr. Wulfraat reported having no conflicts of interest.

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 adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (>6% difference) are shown in Table 2.

Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo

ADVERSE EVENTS %	Placebo Epoprostenol (n = 131)	Revatio Epoprostenol (n = 134)	Placebo-Subtracted %
Headache	34	57	23
Edema [^]	13	25	14
Dyspepsia	2	16	14
Pain in extremity	6	17	11
Diarrhea	18	25	7
Nausea	18	25	7
Nasal congestion	2	9	7

[^]includes peripheral edema

REVATIO Injection

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

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

Decreases in and Loss of Vision

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [see Warnings and Precautions].

Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors [see Warnings and Precautions].

Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

DRUG INTERACTIONS

Nitrates

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

Ritonavir and other Potent CYP3A Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended [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].

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

Amlodipine

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

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 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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 breast 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 drug 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 CL_{Cr} < 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 for up to 24 months at 60 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 vitro* human lymphocytes and *in vivo* mouse micronucleus assays 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 38 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.
- 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.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

RX only

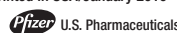
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Joint-Sparing Surgery Helps Ease Deformities

FROM THE AMERICAN ORTHOPAEDIC FOOT AND ANKLE SOCIETY ANNUAL MEETING

NATIONAL HARBOR, MD. — Joint-sparing surgical techniques can reduce pain, increase function, and improve the appearance of lesser metatarsophalangeal joint deformities in patients with severe rheumatoid arthritis, a small retrospective study has shown.

In a survey of 11 patients with RA undergoing joint-sparing surgery, 83% reported improved callosities and shoe wear. Half of the patients reported improved cosmesis, and almost all said they had less pain at rest and less weight-bearing pain after the surgery, Brockford D. Herring, D.O., said at the meeting.

The researchers retrospectively studied preoperative x-rays for dislocations and postoperative x-rays for recurrent dislocations from forefoot RA cases. They identified 11 patients with 30 lesser toe reconstructions and 10 metatarsal shortenings with an average follow-up of 4.7 years.

Among these patients, 60% of lesser toes were dislocated on preoperative x-ray and 30% were re-dislocated on postoperative x-ray. The fourth and fifth toes accounted for two-thirds of re-dislocations. Of the 10 metatarsal shortenings, only 1 was re-dislocated on postoperative x-ray.

The joint-sparing procedure involves metatarsophalangeal capsule release, extensor digitorum longus to extensor digitorum brevis tendon transfer, proximal phalangeal head resection, flexor digitorum longus to extensor tendon transfer through a drill hole in the proximal phalanx, and metatarsal shortening (on occasion).

Two-thirds of patients said their results were excellent, but no one reported changes in gait stability. All patients said that they would recommend the procedure to individuals with RA.

As the disease progresses, these techniques maintain bone stock for later salvage procedures, said Dr. Herring, an orthopedic surgeon in Sarasota, Fla.

—Kerri Wachter

Disclosures: Dr. Herring reported that he has no relevant disclosures.