

VERBATIM

‘The cost of fixing [the system by which physicians are reimbursed] may be high, but the reason it’s high is because the hole is so deep—and we didn’t dig that hole. All we’re asking is to fill in that hole so we’re breaking even.’

Robert Doherty, senior vice president for governmental affairs and public policy with the American College of Physicians, page 30

Biologics Don’t Drive Up Risk of Uveitis in JIA

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SAN ANTONIO — Certain children with juvenile idiopathic arthritis are at risk for developing uveitis, but treatment with biologic agents does not increase this risk, Roetraud K. Saurenmann, M.D., said at the annual meeting of the

American College of Rheumatology. Tumor necrosis factor (TNF)- α therapy has been used successfully to treat pediatric uveitis, but concern has arisen because there have been reports of cases of new-onset JIA-associated uveitis occurring during treatment with these drugs.

In an effort to clarify a possible link between anti-TNF- α treatment and uveitis, Dr. Saurenmann and her colleagues at the Hospital for Sick Children, Toronto, performed a retrospective chart review of all children with a diagnosis of JIA treated at her center between 1996 and 2003.

Among the 1,109 patients identified, 145 had developed uveitis sometime in the course of their disease and so were considered to be at risk for subsequent episodes. Among those with the ocular complication, 87 had been treated with anti-TNF- α therapy.

However, in 17 cases, the uveitis preceded the anti-TNF- α treatment, so a causal effect was ruled out.

In the 70 remaining patients treated with anti-TNF- α therapy, there were 2 cases of new-onset uveitis, both in patients receiving etanercept.

One of the patients with new-onset uveitis had a 4-year history of psoriatic arthritis, and the other patient had had oligoarticular JIA for 6.4 years.

Cox regression analysis was carried out for these 70 patients, using new-onset uveitis as the primary end point and anti-TNF- α as a time-dependent variable.

There was no statistically significant difference in risk of uveitis between patients with and without a history of taking anti-TNF- α therapy, Dr. Saurenmann noted during her presentation.

And when the possible association between uveitis and biologic therapy was analyzed according to JIA subtypes, those with oligoarticular JIA had an increased risk, as did those who were antinuclear antibody (ANA) positive and rheumatoid factor (RF) negative, she said.

Patients who developed JIA at a young age also were at increased risk, and the ocular complication typically occurred early in the course of disease.

Children with psoriatic arthritis also are at risk, but those with RF positive and systemic onset JIA are not.

“So we asked ourselves which at-risk patients would be eligible for anti-TNF- α treatment, and that would be those with oligoarticular disease; those with polyarticular, RF-negative disease; and those with psoriatic JIA,” she said.

A total of 434 patients fell into those groups; 45 of these had received anti-TNF- α treatment.

But once again Cox regression analysis found no difference in risk between those with and without anti-TNF- α treatment, she said.

“We concluded that anti-TNF- α therapy does not alter the risk for the development of new onset uveitis in children with JIA,” she said.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg/day (approximately 0.4-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) for 104 weeks or in mice given oral doses up to 8.0 mg/kg/day (approximately 2.2-fold the human dose, as noted above) for 99 weeks.

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow. Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively (4.9-fold and 2.5-fold the human dose, as noted above). However, an increased incidence of embryofetality at oral doses of 1 mg/kg/day (0.5-fold the human dose, as noted above) was observed in rats when dams were given meloxicam 2 weeks prior to mating and during early embryonic development.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day (84.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and embryofetality at oral doses of 2.5 mg/kg/day (5-fold the human dose, as noted above) when rabbits were treated throughout organogenesis. Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.2-fold the human dose, as noted above) throughout organogenesis. An increased incidence of stillbirths was observed when rats were given oral doses of 1 mg/kg/day throughout organogenesis. Meloxicam crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. MOBIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Meloxicam caused a reduction in birth index, live births, and neonatal survival at oral doses of 2.0, 125 mg/kg/day (approximately 0.07-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) when rats were treated during the late gestation and lactation period. No studies have been conducted to evaluate the effect of meloxicam on the closure of the ductus arteriosus in humans; use of meloxicam during the third trimester of pregnancy should be avoided.

Labor and Delivery

Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of stillbirths, increased length of delivery time, and delayed parturition at oral dosages of 2.1 mg/kg/day (approximately 0.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion), and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1-fold the human dose, as noted above) throughout organogenesis. Similar findings were observed in rats receiving oral dosages of 2.0, 125 mg/kg/day (approximately 0.07-fold the human dose, as noted above) during late gestation and the lactation period.

Nursing Mothers

Studies of meloxicam excretion in human milk have not been conducted; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because of the potential for serious adverse reactions in nursing infants from MOBIC, 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 in pediatric patients under 18 years of age have not been established.

Geriatric Use

Caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS

The MOBIC phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3525 OA patients and 1351 RA patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 681 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in placebo and/or active-controlled osteoarthritis trials and 2363 of these patients were treated in two placebo and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of MOBIC with placebo.

The following adverse events (%) occurred in 2 of MOBIC 7.5 mg daily (n=154) and 15 mg daily (n=150) patients, respectively, in a 12-week osteoarthritis placebo- and active-controlled trial: abdominal pain, 1.9%, 2.6%; diarrhea, 1.8%, 3.2%; dyspepsia, 4.5%, 4.5%; flatulence, 3.2%, 3.2%; nausea, 3.9%, 3.8%; accident/household, 4.5%, 3.2%; edema, 1.9%, 4.5%; fall, 0.6%, 0.0%; influenza-like symptoms, 4.5%, 5.8%; dizziness, 2.6%, 3.8%; headache, 7.8%, 8.3%; pharyngitis, 0.6%, 3.2%; upper respiratory tract infection, 3.2%, 1.9%; rash, 2.6%, 0.6%.

The following adverse events (%) occurred with MOBIC 7.5 mg daily in 2 of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.7%, 4.7%; constipation, 0.6%, 1.9%; diarrhea, 1.9%, 0.9%; dyspepsia, 3.8%, 8.9%; flatulence, 0.5%, 3.0%; nausea, 2.4%, 4.7%; vomiting, 0.6%, 1.8%; edema, 1.0%, 2.4%; pain, 0.9%, 3.6%; dizziness, 1.1%, 2.4%; headache, 2.4%, 3.6%; anemia, 0.1%, 4.1%; arthralgia, 0.5%, 5.3%; back pain, 0.5%, 3.0%; insomnia, 0.4%, 3.0%; coughing, 0.8%, 1.0%; upper respiratory tract infection, 0.2%, 8.3%; pruritus, 0.4%, 2.4%; rash, 0.3%, 3.0%; micturition frequency, 0.1%, 2.4%; urinary tract infection, 0.3%, 4.7%.

The following adverse events (%) occurred with MOBIC 15 mg daily in 2 of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.3%, 2.9%; constipation, 1.2%, 2.6%; diarrhea, 2.7%, 2.6%; dyspepsia, 3.4%, 9.5%; flatulence, 0.4%, 0.6%; nausea, 4.7%, 7.2%; vomiting, 0.8%, 2.6%; edema, 2.0%, 1.6%; pain, 2.0%, 5.2%; dizziness, 1.6%, 2.6%; headache, 2.7%, 2.6%; anemia, 0.0%, 2.9%; arthralgia, 0.0%, 1.3%; back pain, 0.4%, 0.7%; insomnia, 0.0%, 1.0%; coughing, 0.8%, 1.0%; upper respiratory tract infection, 0.2%, 7.5%; pruritus, 1.2%, 0.0%; rash, 1.2%, 1.3%; micturition frequency, 0.4%, 1.3%; urinary tract infection, 0.4%, 6.9%.

WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined. WHO preferred terms rash, rash erythematous and rash maculo-papular combined.

The following adverse events (%) occurred respectively with MOBIC 7.5 and 15 mg daily in 2 of patients treated in two 12-week rheumatoid arthritis placebo controlled trials: abdominal pain NOS, 2.9%, 3.3%; NCS, 4.9%, 3.4%; upper respiratory tract infection (signs and symptoms), 5.8%, 4.0%; nausea, 3.3%, 3.8%; influenza like illness, 2.9%, 2.3%; upper respiratory tract infections-pathogen class unspecified, 7.0%, 6.5%; joint related signs and symptoms, 1.5%, 2.3%; musculoskeletal and connective tissue signs and symptoms NOS, 1.7%, 2.9%; headaches NOS, 6.4%, 5.5%; dizziness (except vertigo), 2.3%, 0.4%; rash NOS, 1.0%, 2.1%.

MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (arthritis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling), and musculoskeletal and connective tissue signs and symptoms NEC (back pain, back pain aggravated, muscle spasms, musculoskeletal pain).

²MedDRA preferred term: diarrhea NOS, abdominal pain NOS, influenza like illness, headaches NOS, dizziness (except vertigo), and rash NOS.

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore the daily dose of MOBIC should not exceed 15 mg.

The following is a list of adverse drug reactions occurring in <2% of patients receiving MOBIC in clinical trials involving approximately 16,200 patients. Adverse reactions reported only in worldwide post-marketing experience of the literature are shown in italics and are considered rare (<0.1%).

Body as a Whole: allergic reaction, anaphylactoid reactions including shock, face edema, fatigue, fever, hot flashes, malaise, syncope, weight decrease, weight increase. **Cardiovascular:** angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis.

Gastrointestinal: colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastroenteric hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, peritonitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis, ulcerative.

Heart Rate and Rhythm: arrhythmia, palpitation, tachycardia. **Hematologic:** agranulocytosis, leukopenia, purpura, thrombocytopenia. **Liver and Biliary System:** ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, jaundice.

Metabolic and Nutritional: dehydration. **Psychiatric Disorders:** abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence. **Respiratory:** asthma, bronchospasm, dyspnea. **Skin and Appendages:** alopecia, angiodedema, bullous eruption, erythema multiforme, photosensitivity reaction, pruritus, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis, urticaria. **Special Senses:** abnormal vision, conjunctivitis, taste perversion, tinnitus. **Urinary System:** albuminuria, BUN increased, creatinine increased, hematuria, interstitial nephritis, renal failure.

OVERDOSAGE

There is limited experience with meloxicam overdose. Four cases have taken 6 to 11 times the highest recommended dose, all recovered. Cholestyramine is known to accelerate the clearance of meloxicam.

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, gastric lavage followed by activated charcoal is recommended. Gastric lavage performed more than one hour after overdose has little benefit in the treatment of overdose. Administration of activated charcoal is recommended for patients who present 1-2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. Accelerated removal of meloxicam by 4 gm oral doses of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdose. Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Pharmacokinetics

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