

Treat Oligoarthritis to Prevent Limb Shortening

BY SALLY KOCH KUBETIN

SANTA MONICA, CALIF. — There is only one cause of joint inflammation in childhood that the child will typically outgrow: true oligoarthritis. Even though the inflammation will eventually pass, affected children still need treatment to prevent limb-length discrepancy or blindness resulting from uveitis, according to Dr. Thomas J.A. Lehman.

Because of the shortage of pediatric rheumatologists, adult rheumatologists often end up treating children with new-onset joint symptoms, he noted at the meeting sponsored by RHEUMATOLOGY NEWS and Skin Disease Education Foundation.

Without genetic markers, it is difficult to separate all the types of arthritis—which are not limited to just the eight subtypes listed in the official diagnostic

criteria—that occur in children. “There may be anywhere from 30 to 50 subtypes” of arthritis in children. This matters, because they will not all respond to the same treatment or have the same disease course, said Dr. Lehman, chief of the division of pediatric rheumatology at the Hospital for Special Surgery in New York.

Oligoarthritis is not a systemic disease, which makes it harder to diagnose

early. The onset of joint swelling and pain should be limited to four or fewer large joints during the first 6 months, and most often only a single joint is affected. Because the stiffness and pain are worse upon awakening and tend to ease as the day progresses, parents often let it continue awhile and often cannot pinpoint when the symptoms started. Also, onset usually occurs at age 1-5 years (and typical oligoarthritis never begins after age 9 years), which means that the children are too young to describe their symptoms. A limp in the morning and a swollen knee may be the only sign that something is wrong; sometimes a visiting grandmother notices what the parents have overlooked.

Laboratory findings—or lack thereof—can help confirm the diagnosis. Because this is not a systemic disease, the hemoglobin level is never less than 11.0 g/dL and the erythrocyte sedimentation rate is never greater than 40 mm/h, according to Dr. Lehman. There is never fever, rash, or elevated white blood cell count. Oligoarthritis affects more girls than boys. The children are often positive for antinuclear antibodies and often have eye disease, usually uveitis.

It is important to make the diagnosis of true oligoarthritis as early as possible, according to Dr. Lehman. Too many children are allowed to continue limping without a diagnosis because some criteria require joint pain for at least 6 weeks and others say 3 months. That doesn't mean children can't be treated before a definitive diagnosis of oligoarthritis is made, he said. Continued pain produces muscle loss and joint damage. In addition, it hinders a child's emotional development when they can't keep up with their friends and participate in normal activities.

Many children with true oligoarthritis will respond to NSAIDs, but physicians should not be afraid to use all the medication necessary to control the disease. Corticosteroid injections may be helpful if there is a single “stubborn” joint.

This arthritis never involves the fingers or hips and never more than four joints. “True oligoarthritis affects only the knees,” said Dr. Lehman, who stressed that these diagnostic criteria are his own and are not accepted by any accrediting body. Some children with a swollen and painful ankle, wrist, or elbow may have oligoarthritis, but children with these joints involved are much less likely to “grow out of it.”

Children who present after age 9 years or who have involvement of four or fewer joints that expand to more than four joints do not have true oligoarthritis. Theirs is likely to be a debilitating arthritis, and they will not outgrow it, he stressed. “You need to be very aggressive and careful” in their management.

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In addition to the adverse events in the table, the following events occurred at a rate of $\geq 1\%$ but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with Micardis® (telmisartan) tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with MICARDIS monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to MICARDIS tablets:

Autonomic Nervous System: impotence, increased sweating, flushing; **Body as a Whole:** allergy, fever, leg pain, malaise; **Cardiovascular:** palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; **CNS:** insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia; **Gastrointestinal:** flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; **Metabolic:** gout, hypercholesterolemia, diabetes mellitus; **Musculoskeletal:** arthritis, arthralgia, leg cramps; **Psychiatric:** anxiety, depression, nervousness; **Resistance Mechanism:** infection, fungal infection, abscess, otitis media; **Respiratory:** asthma, bronchitis, rhinitis, dyspnea, epistaxis; **Skin:** dermatitis, rash, eczema, pruritus; **Urinary:** micturition frequency, cystitis; **Vascular:** cerebrovascular disorder; and **Special Senses:** abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Cardiovascular Risk Reduction

Because common adverse reactions were well characterized in studies of telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of telmisartan for cardiovascular risk reduction. In TRANSCEND (N=5926, 4 years and 8 months of follow-up), discontinuations for adverse events were 8.4% on telmisartan and 7.6% on placebo. The only serious adverse events at least 1% more common on telmisartan than placebo were intermittent claudication (7% vs 6%) and skin ulcer (3% vs 2%).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of MICARDIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to MICARDIS.

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including MICARDIS.

DRUG INTERACTIONS

Digoxin: When MICARDIS was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when

initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including MICARDIS. Therefore, monitor serum lithium levels during concomitant use.

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use of MICARDIS and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters). See Warnings and Precautions.

Nursing Mothers

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients receiving MICARDIS in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients 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.

Of the total number of patients receiving MICARDIS in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥ 65 to < 75 years of age was 42%; 15% of patients were ≥ 75 years old. No overall differences in effectiveness and safety were observed in these patients compared to younger patients 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.

Hepatic Insufficiency

Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with MICARDIS tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Rx only



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