

Migratory Arthritis? Rule Out Childhood Leukemia

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Physicians should rule out leukemia when evaluating children with migratory arthritis, David D. Sherry, M.D., reported at a symposium sponsored by the American College of Rheumatology.

Acute lymphatic leukemia is the most common childhood systemic malignancy associated with musculoskeletal pain and/or arthritis, and its clinical features

can often mimic those of juvenile idiopathic arthritis.

In about 50% of cases, the correct diagnosis is delayed.

Patients with leukemia may have very painful arthritis or arthralgia that is usually migratory or episodic. It can occur in one or more joints, including the hip or joints such as the talus-cuboid joint, which is rarely involved in juvenile arthritis, he said.

Other symptoms include low-grade

fever and body aches that are accentuated by weight bearing.

"These kids have to be carried, and you don't carry kids with RA generally," said Dr. Sherry, director of clinical rheumatology at the Children's Hospital of Philadelphia.

Systemic symptoms are present at or near onset of disease. But hematologic abnormalities may take time to develop. One early warning signal is an elevated erythrocyte sedimentation rate, which

may be present without other inflammatory markers, he said.

In a case involving a 5-year-old boy, the white blood count was normal, but the erythrocyte sedimentation rate was 89 mm/hr—well above the normal range of 1 mm/hr to 13 mm/hr for males.

A plain radiograph of his swollen knee revealed a grey leukemic line. Metaphyseal bands may be present on x-ray, as well as osteopenia, cortical or periosteal lesions, and osteolytic reaction.

Physicians also should be watchful for leukemia in children with hip disease or Down syndrome, he said.



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Brief Summary
Consult package insert for full prescribing information.

INDICATIONS AND USAGE: Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome.

CONTRAINDICATIONS: Cevimeline is contraindicated in patients with uncontrolled asthma, known hypersensitivity to cevimeline, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle-closure) glaucoma.

WARNINGS:

Cardiovascular Disease: Cevimeline can potentially alter cardiac conduction and/or heart rate. Patients with significant cardiovascular disease may potentially be unable to compensate for transient changes in hemodynamics or rhythm induced by EVOXAC®. EVOXAC® should be used with caution and under close medical supervision in patients with a history of cardiovascular disease evidenced by angina pectoris or myocardial infarction.

Pulmonary Disease: Cevimeline can potentially increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Cevimeline should be administered with caution and with close medical supervision to patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

Ocular: Ophthalmic formulations of muscarinic agonists have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

PRECAUTIONS:

General: Cevimeline toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors. Cevimeline should be administered with caution to patients with a history of nephrolithiasis or cholelithiasis. Contractions of the gallbladder or biliary smooth muscle could precipitate complications such as cholecystitis, cholangitis and biliary obstruction. An increase in the ureteral smooth muscle tone could theoretically precipitate renal colic or ureteral reflux in patients with nephrolithiasis.

Information for Patients: Patients should be informed that cevimeline may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking cevimeline, dehydration may develop. The patient should drink extra water and consult a health care provider.

Drug Interactions: Cevimeline should be administered with caution to patients taking beta adrenergic antagonists, because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with cevimeline can be expected to have additive effects. Cevimeline might interfere with desirable antimuscarinic effects of drugs used concomitantly.

Drugs which inhibit CYP2D6 and CYP3A4 also inhibit the metabolism of cevimeline. Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events. In an *in vitro* study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Lifetime carcinogenicity studies were conducted in CD-1 mice and F-344 rats. A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100 mg/kg/day (approximately 8 times the maximum human exposure based on comparison of AUC data). No other significant differences in tumor incidence were observed in either mice or rats.

Cevimeline exhibited no evidence of mutagenicity or clastogenicity in a battery of assays that included an Ames test, an *in vitro* chromosomal aberration study in mammalian cells, a mouse lymphoma study in L5178Y cells, or a micronucleus assay conducted *in vivo* in ICR mice.

Cevimeline did not adversely affect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45 mg/kg/day (approximately 5 times the maximum recommended dose for a 60 kg human following normalization of the data on the basis of body surface area estimates). Females that were treated with cevimeline at dosages up to 45 mg/kg/day from 14 days prior to mating through day seven of gestation exhibited a statistically significantly smaller number of implantations than did control animals.

Pregnancy: Pregnancy Category C.

Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45 mg/kg/day (approximately 5 times the maximum recommended dose for a 60 kg human when compared on the basis of body surface area estimates). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Cevimeline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from EVOXAC®, a decision should be made 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: Although clinical studies of cevimeline included subjects over the age of 65, the numbers were not sufficient to determine whether they respond differently from younger subjects. Special care should be exercised when cevimeline treatment is initiated in an elderly patient, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly.

ADVERSE REACTIONS: Cevimeline was administered to 1777 patients during clinical trials worldwide, including Sjögren's patients and patients with other conditions. In placebo-controlled Sjögren's studies in the U.S., 320 patients received cevimeline doses ranging from 15 mg tid to 60 mg tid, of whom 53% were women and 7% were men. Demographic distribution was 90% Caucasian, 5% Hispanic, 3% Black, and 2% of other origin. In these studies, 14.6% of patients discontinued treatment with cevimeline due to adverse events.

The following adverse events associated with muscarinic agonism were observed in the clinical trials of cevimeline in Sjögren's syndrome patients:

Adverse Event	Cevimeline	Placebo	Adverse Event	Cevimeline	Placebo
	30 mg (tid) n=533	(tid) n=164		30 mg (tid) n=533	(tid) n=164
Excessive Sweating	18.7%	2.4%	Urinary Frequency	0.9%	1.8%
Nausea	13.8%	7.9%	Asthenia	0.5%	0.0%
Rhinitis	11.2%	5.4%	Flushing	0.3%	0.6%
Diarrhea	10.3%	10.3%	Polyuria	0.1%	0.6%
Excessive Salivation	2.2%	0.6%			

*n is the total number of patients exposed to the dose at any time during the study

In addition, the following adverse events (3% incidence) were reported in the Sjögren's clinical trials:

Adverse Event	Cevimeline	Placebo	Adverse Event	Cevimeline	Placebo
	30 mg (tid) n=533	(tid) n=164		30 mg (tid) n=533	(tid) n=164
Headache	14.4%	20.1%	Conjunctivitis	4.3%	3.6%
Sinusitis	12.3%	10.9%	Dizziness	4.1%	7.3%
Upper Respiratory			Bronchitis	4.1%	1.2%
Tract Infection	11.4%	9.1%	Arthralgia	3.7%	1.8%
Dyspepsia	7.8%	8.5%	Surgical Intervention	3.3%	3.0%
Abdominal Pain	7.6%	6.7%	Fatigue	3.3%	1.2%
Urinary Tract Infection	6.1%	3.0%	Pain	3.3%	3.0%
Coughing	6.1%	3.0%	Skeletal Pain	2.8%	1.8%
Pharyngitis	5.2%	5.4%	Insomnia	2.4%	1.2%
Vomiting	4.6%	2.4%	Hot Flashes	2.4%	0.0%
Injury	4.5%	2.4%	Rigors	1.3%	1.2%
Back Pain	4.5%	4.2%	Anxiety	1.3%	1.2%
Rash	4.3%	6.0%			

*n is the total number of patients exposed to the dose at any time during the study

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The following events were reported in Sjögren's patients at incidences of <3% and 1%: constipation, tremor, abnormal vision, hypertension, peripheral edema, chest pain, myalgia, fever, anorexia, eye pain, earache, dry mouth, vertigo, salivary gland pain, pruritus, influenza-like symptoms, eye infection, post-operative pain, vaginitis, skin disorder, depression, hiccup, hyporeflexia, infection, fungal infection, sialoadenitis, otitis media, erythematous rash, pneumonia, edema, salivary gland enlargement, allergy, gastroesophageal reflux, eye abnormality, migraine, tooth disorder, epistaxis, flatulence, toothache, ulcerative stomatitis, anemia, hyposthesia, cystitis, leg cramps, abscess, eruption, moniliasis, palpitation, increased amylase, xerophthalmia, allergic reaction.

The following events were reported rarely in treated Sjögren's patients (<1%): Causal relation is unknown:

Body as a Whole Disorders: aggravated allergy, precordial chest pain, abnormal crying, hematoma, leg pain, edema, periorbital edema, activated pain trauma, pallor, changed sensation to temperature, weight decrease, weight increase, choking, mouth edema, syncope, malaise, face edema, substernal chest pain

Cardiovascular Disorders: abnormal ECG, heart disorder, heart murmur, aggravated hypertension, hypotension, arrhythmia, extrasystoles, t wave inversion, tachycardia, supraventricular tachycardia, angina pectoris, myocardial infarction, pericarditis, pulmonary embolism, peripheral ischemia, superficial phlebitis, purpura, deep thrombophlebitis, vascular disorder, vasculitis, hypertension

Digestive Disorders: appendicitis, increased appetite, ulcerative colitis, diverticulitis, duodenitis, dysphagia, enterocolitis, gastric ulcer, gastritis, gastroenteritis, gastrointestinal hemorrhage, gingivitis, glossitis, rectum hemorrhage, hemorrhoids, ileus, irritable bowel syndrome, melena, mucositis, esophageal stricture, esophagitis, oral hemorrhage, peptic ulcer, periodontal destruction, retinal disorder, stomatitis, tenesmus, tongue discoloration, tongue disorder, geographic tongue, tongue ulceration, dental caries

Endocrine Disorders: increased glucocorticoids, goiter, hypothyroidism

Hematologic Disorders: thrombocytopenic purpura, thrombocytemia, thrombocytopenia, hypochromic anemia, eosinophilia, granulocytopenia, leukopenia, leukocytosis, cervical lymphadenopathy, lymphadenopathy

Liver and Biliary System Disorders: cholelithiasis, increased gamma-glutamyl transferase, increased hepatic enzymes, abnormal hepatic function, viral hepatitis, increased serum glutamate oxaloacetate transaminase (SGOT) (also called AST-aspartate aminotransferase), increased serum glutamate pyruvate transaminase (SGPT) (also called ALT-alanine aminotransferase)

Metabolic and Nutritional Disorders: dehydration, diabetes mellitus, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, thirst

Musculoskeletal Disorders: arthritis, aggravated arthritis, arthropathy, femoral head avascular necrosis, bone disorder, bursitis, costochondritis, plantar fasciitis, muscle weakness, osteomyelitis, osteoporosis, synovitis, tendinitis, tenosynovitis

Neoplasms: basal cell carcinoma, squamous carcinoma

Nervous Disorders: carpal tunnel syndrome, coma, abnormal coordination, dysesthesia, dyskinesia, dysphonia, aggravated multiple sclerosis, involuntary muscle contractions, neuralgia, neuropathy, paresthesia, speech disorder, agitation, confusion, depersonalization, aggravated depression, abnormal dreaming, emotional lability, manic reaction, paranoia, somnolence, abnormal thinking, hyperkinesia, hallucination

Miscellaneous Disorders: fall, food poisoning, heat stroke, joint dislocation, post-operative hemorrhage

Resistance Mechanism Disorders: cellulitis, herpes simplex, herpes zoster, bacterial infection, viral infection, genital moniliasis, sepsis

Respiratory Disorders: asthma, bronchospasm, chronic obstructive airway disease, dyspnea, hemoptysis, laryngitis, nasal ulcer, pleural effusion, pleurisy, pulmonary congestion, pulmonary fibrosis, respiratory disorder

Rheumatologic Disorders: aggravated rheumatoid arthritis, lupus erythematosus rash, lupus erythematosus syndrome

Skin and Appendages Disorders: acne, alopecia, burn, dermatitis, contact dermatitis, lichenoid dermatitis, eczema, furunculosis, hyperkeratosis, lichen planus, nail discoloration, nail disorder, onychia, onychomycosis, paronychia, photosensitivity reaction, rosacea, scleroderma, seborrhea, skin discoloration, dry skin, skin exfoliation, dry skin, skin hypertrophy, skin ulceration, urticaria, verruca, buccial eruption, cold clammy skin

Special Senses Disorders: deafness, decreased hearing, motion sickness, parosmia, taste perversion, blepharitis, cataract, corneal opacity, corneal ulceration, diplopia, glaucoma, anterior chamber eye hemorrhage, keratitis, keratoconjunctivitis, mydriasis, myopia, photopsia, retinal deposits, retinal disorder, scleritis, vitreous detachment, tinnitus

Urogenital Disorders: epididymitis, prostatic disorder, abnormal sexual function, amenorrhea, female breast neoplasm, malignant female breast neoplasm, female breast pain, positive cervical smear test, dysmenorrhea, uterine disorder, intermenstrual bleeding, leukorrhea, menorrhagia, menstrual disorder, ovarian cyst, ovarian disorder, genital pruritus, uterine hemorrhage, vaginal hemorrhage, atrophic vaginitis, albuminuria, bladder discomfort, increased blood urea nitrogen, dysuria, hematuria, micturition disorder, nephrosis, nocturia, increased nonprotein nitrogen, pyelonephritis, renal calculus, abnormal renal function, renal pain, stranguary, urethral disorder, abnormal urine, urinary incontinence, decreased urine flow, pyuria

In one subject with lupus erythematosus receiving concomitant multiple drug therapy, a highly elevated ALT level was noted after the fourth week of cevimeline therapy. In two other subjects receiving cevimeline in the clinical trials, very high AST levels were noted. The significance of these findings is unknown.

Additional adverse events (relationship unknown) which occurred in other clinical studies (patient population different from Sjögren's patients) are as follows:

cholelithic syndrome, blood pressure fluctuation, cardiomegaly, postural hypotension, aphasia, convulsions, abnormal gait, hyperesthesia, paralysis, abnormal sexual function, enlarged abdomen, change in bowel habits, gum hyperplasia, intestinal obstruction, bundle branch block, increased creatine phosphokinase, electrolyte abnormality, glycosuria, gout, hyperkalemia, hyperproteinemia, increased lactic dehydrogenase (LDH), increased alkaline phosphatase, failure to thrive, abnormal platelets, aggressive reaction, amnesia, apathy, delirium, dementia, illusion, impotence, neurosis, paranoid reaction, personality disorder, hyperhemoglobinemia, apnea, atelectasis, yawning, oliguria, urinary retention, distended vein, lymphocytosis

MANAGEMENT OF OVERDOSE: Management of the signs and symptoms of acute overdose should be handled in a manner consistent with that indicated for other muscarinic agonists: general supportive measures should be instituted. If medically indicated, atropine, an anti-cholinergic agent may be of value as an antidote for emergency use in patients who have had an overdose of cevimeline. If medically indicated, epinephrine may also be of value in the presence of severe cardiovascular depression or bronchospasm. It is not known if cevimeline is dialyzable.

DOSSAGE AND ADMINISTRATION: The recommended dose of cevimeline hydrochloride is 30 mg taken three times a day. There is insufficient safety information to support doses greater than 30 mg tid. There is also insufficient evidence for additional efficacy of cevimeline hydrochloride at doses greater than 30 mg tid.

Rx Only

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Osteogenesis Imperfecta Function Tied to BMD Levels

Functional outcome and ability in children with osteogenesis imperfecta, Robert Huang, M.D., reported at the annual meeting of the American Academy of Orthopaedic Surgeons.

The findings lend credence to a current focus in treatment on improving bone mineral density (BMD) in children who are afflicted with osteogenesis imperfecta.

"Bisphosphonates have come to the forefront of treatment for osteogenesis imperfecta, but [we haven't known] the relationship of BMD ultimately to function," said Dr. Huang of Houston Shriners Hospital.

Dr. Huang and his associates conducted a review of the records of 29 consecutive patients with osteogenesis imperfecta (ages 4-17) who underwent BMD assessment (mostly of the lumbar spine and wrist) using dual-energy x-ray absorptiometry (DXA). He and his coinvestigators then analyzed functional outcomes data that were collected using the Pediatric Outcomes Data Collection Instrument (PODCI).

Their analysis of scores obtained from parent PODCI forms revealed that there were significant relationships between lumbar spine BMD and upper extremity function. In addition, an analysis of scores that were obtained from the child PODCI scores (15 children were old enough to complete the child PODCI forms) revealed that there were significant relationships between wrist BMD and upper extremity function.

The investigators also found relationships between BMD and other functional domains within PODCI. "Certainly, BMD is an indicator of physical function," Dr. Huang said.

DXA scanning is increasingly being used as a means of obtaining baseline measurements and for monitoring patients with osteogenesis imperfecta, but more "BMD data for children with osteogenesis imperfecta will be required to establish specific guidelines for the treatment of children with [the disorder]," he said.

—Christine Kilgore