

Etanercept Shown Superior to Methotrexate in JIA

BY JANE SALODOF MACNEIL
Southwest Bureau

VERSAILLES, FRANCE — Etanercept was more effective than methotrexate in reducing inflammation and radiographic progression in a retrospective study of juvenile idiopathic arthritis presented at the 12th European Pediatric Rheumatology Congress.

Although 40 children on etanercept (Enbrel) therapy were sicker at baseline, Su-

san Nielsen, M.D., reported they demonstrated significantly greater improvement at 12 months, compared with 67 children treated with methotrexate.

"Both groups did improve over 1 year, but the etanercept group improved the most," said Dr. Nielsen of the Juliane Marie Centret, Rigshospitalet, Copenhagen. A member of the national coordinating committee of the Pediatric Rheumatology International Trials Organization (PRINTO), she presented the data

on behalf of the Italian Pediatric Rheumatology Study Group.

Nearly 80% of the children on etanercept met the American College of Rheumatology's definition of 30% improvement. About half reached the standard for 70% improvement.

At 1 year, fewer than half of the children on methotrexate satisfied the definition of 30% improvement; roughly a third achieved 70% improvement, according to Dr. Nielsen's presentation.

The investigators mined an Italian registry of patients treated with etanercept from March 1999 to January 2004. They compared the children selected with a historical control group of patients who received methotrexate as monotherapy from September 1989 to October 2003.

All patients included in the analysis were required to have had a wrist x-ray at baseline and at 1 year. These imaging results were used to measure radiographic progression according to Poznanski scores.

Coinvestigator Angelo Ravelli, M.D., of Istituto G. Gaslini in Genoa, Italy, told this newspaper that the Poznanski scoring was important to the study because it provided a reliable way to measure changes in children who were also growing during the course of the study.

The longer duration of disease might explain why the etanercept patients showed less radiographic progression.

"Children grow, so the appearance of bone and width of the joints varies with age," he said. "Just looking at the film of children of different ages you can't estimate rightly the amount of damage. ... You need a normal standard."

Indeed, the difference in average changes in Poznanski scores proved statistically significant. Scores fell by -0.023 in the children on methotrexate, but rose by 0.389 in the children on etanercept. At baseline, the mean scores were 1.25 for the methotrexate group and -2.24 in the etanercept cohort.

Other statistically significant changes included greater improvements on a parental global visual analog scale (-4.8 with etanercept vs. -1.4 with methotrexate), in the Childhood Health Assessment Questionnaire (-0.9 vs. -0.2), in the number of active joints (-8.0 vs. -4.0), and in the number of joints with limitation of motion (-6.0 vs. -2.0).

At the start of treatment, a number of measures suggested that the etanercept patients had worse disease. They had been sick longer on average: 4.9 years vs. 2.2 years for the methotrexate group. Their parental global assessment scores were higher (5.87 vs. 3.98), as were their Childhood Health Assessment Questionnaire scores (1.4 vs. 0.78). The etanercept patients also had more joints with restricted motion (13.3 vs. 9.2).

The investigators acknowledged that longer duration of disease might offer a partial explanation for why the etanercept patients showed less radiographic progression. They called for a controlled clinical trial to compare the two drugs.

Observational studies don't prove anything, Dr. Nielsen said. "But we think etanercept is superior to methotrexate in suppressing inflammation and may be superior in reducing radiographic progression."

"If the patients with etanercept were worse than the patients with methotrexate, we think the effect is bigger," added senior scientist Nicola Ruperto, M.D., of PRINTO and Istituto G. Gaslini in an interview after the presentation.



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Brief Summary
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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 93% 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 30 mg (tid) n=533		Placebo (tid) n=164	
	Cevimeline 30 mg (tid) n=533	Placebo (tid) n=164	Cevimeline 30 mg (tid) n=533	Placebo (tid) n=164
Excessive Sweating	18.7%	2.4%	0.9%	1.8%
Nausea	13.8%	7.9%	0.5%	0.0%
Rhinitis	11.2%	5.4%	0.3%	0.6%
Diarrhea	10.3%	10.3%	0.1%	0.6%
Excessive Salivation	2.2%	0.6%		
Urinary Frequency			0.9%	1.8%
Asthenia			0.5%	0.0%
Flushing			0.3%	0.6%
Polyuria			0.1%	0.6%

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

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

Adverse Event	Cevimeline 30 mg (tid) n=533		Placebo (tid) n=164	
	Cevimeline 30 mg (tid) n=533	Placebo (tid) n=164	Cevimeline 30 mg (tid) n=533	Placebo (tid) n=164
Headache	14.4%	20.1%	4.3%	3.6%
Sinusitis	12.3%	10.9%	4.1%	7.2%
Upper Respiratory Tract Infection	11.4%	9.1%	4.1%	1.8%
Dyspepsia	7.8%	8.5%	3.7%	3.0%
Abdominal Pain	7.6%	6.7%	3.3%	1.2%
Urinary Tract Infection	6.1%	3.0%	3.3%	3.0%
Coughing	6.1%	3.0%	2.8%	1.8%
Pharyngitis	5.2%	5.4%	2.4%	1.2%
Vomiting	4.6%	2.4%	2.4%	0.0%
Injury	4.5%	2.4%	1.3%	1.2%
Back Pain	4.5%	4.2%	1.3%	1.2%
Rash	4.3%	6.0%	1.3%	1.2%

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

The following events were reported in Sjögren's patients at incidences of <3% and ≥1%: constipation, tremor, abnormal vision, hypertonia, 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, hyoaxreflexia, 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, hypospasmia, 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, rectal disorder, stomatitis, tenesmus, tongue discoloration, tongue disorder, geographic tongue, tongue ulceration, dental caries

Endocrine Disorders: increased glucocorticoids, goiter, hypothyroidism

Hematologic Disorders: thrombocytopenic purpura, thrombocythemia, thrombocytopenia, hypochromic anemia, eosinophilia, granulocytopenia, leucopenia, 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, hyperlipidemia, 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 System 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, parosmia, 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, skin hypertrophy, skin ulceration, urticaria, verruca, bulbous 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, endometrial disorder, intermenstrual bleeding, leukorrhea, menorrhagia, menstrual disorder, ovarian cyst, ovarian disorder, genital pruritus, uterine hemorrhage, vaginal vaginitis, albuminuria, bladder dysfunction, 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:

cholinergic 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, delusion, dementia, illusion, impotence, neurosis, paranoid reaction, personality disorder, hyperhemoglobinemia, apnea, atelectasis, yawning, oliguria, urinary retention, distended vein, lymphocytosis

Post-Marketing Adverse Events: cholecystitis

MANAGEMENT OF OVERDOSE: Management of the signs and symptoms of acute overdosage 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 bronchoconstriction. It is not known if cevimeline is dialyzable.

DOSAGE 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.

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