

Response of AS to Etanercept Maintained at 2 Years

BY NANCY WALSH
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SAN ANTONIO — The clinical safety and efficacy of etanercept persist for more than 2 years in patients with active ankylosing spondylitis, according to the results of an open-label extension study.

Among 26 patients who entered the open, observational phase following a 12-week blinded study, 21 have continued with etanercept, 25 mg twice weekly, for

an additional 102 weeks, Xenofon Baraliakos, M.D., said at the annual meeting of the American College of Rheumatology.

Response was evaluated according to a core set of end points proposed by the Assessments in Ankylosing Spondylitis (ASAS) working group. These included the Bath AS Disease Activity Index (BASDAI) and the ASAS 40, which represents a 40% improvement in several disease domains such as pain, function, and inflammation.

The primary end point was an improvement of 50% or more on the BASDAI, a 10-point visual analog scale that assesses fatigue, spinal pain, peripheral arthritis, anesthesitis, and morning stiffness.

At 102 weeks, an intent-to-treat analysis of all 26 patients indicated that 54% maintained both a BASDAI 50% response and an ASAS 40. At week 54, the corresponding percentages were 58% and 62%, said Dr. Baraliakos, who is of the department of rheumatology, Benjamin

Franklin Hospital, Free University Berlin.

An analysis that included only the 21 study completers also found that disease activity improved significantly, with a mean BASDAI score of 2.7 at week 102. The baseline BASDAI score in this group of patients had been 6.3, on a 0-10 scale, with 10 being the most severe, Dr. Baraliakos said in a poster session.

The mean C-reactive protein level at week 102 was 5 mg/dL, and the mean erythrocyte sedimentation rate was 9 mg/dL, which represented significant improvements over baseline levels, which had been 15.3 and 22.8, respectively. Similar improvements also were seen on the Bath AS functional and mobility indexes.

This study differed from previous investigations of etanercept in AS in that no concomitant corticosteroids or disease-modifying antirheumatic drugs (DMARDs) were permitted. In an earlier study, 40 patients were treated with the tumor necrosis factor- α blocking agent but were allowed to continue other medications (N. Engl. J. Med. 2002;346:1349-56).

In an interim analysis, the authors of this latest study noted that it was important to evaluate etanercept alone (Arthritis Rheum. 2003;48:1667-75).

Pain in Elderly A Risk Factor For Depression

WASHINGTON — The presence of pain in older adults is a significant risk factor for clinical depression, Stephen Harkins, Ph.D., said at the annual meeting of the Gerontological Society of America.

Poorly managed pain lowers quality of life in older persons across cultures, said Dr. Harkins, professor in the departments of gerontology, psychiatry, and biomedical engineering at Virginia Commonwealth University in Richmond.

He reviewed data on 2,900 adults (mean age 75 years) from the National Health and Nutrition Examination Survey and 2,081 adults (mean age 78 years) from the Australian Longitudinal Study on Aging. Both studies included data on musculoskeletal pain, including swollen joints and hip, back, knee, and neck pain.

Mean scores on the Center for Epidemiologic Studies-Depression (CES-D) scale were similar for older adults in the United States (9.3) and Australia (8.2). Overall, 47% of the adults surveyed reported pain in the past week, and the risk of depression was independently related to the presence, type, and number of musculoskeletal problems. In addition, reports of pain more than doubled an individual's risk for exceeding a score of 20 on the CES-D—the cutoff point for clinical depression.

“The take-home message is that pain increases the probability of scoring high on a depression scale,” said Dr. Harkins, who also is director of the psychophysiology and memory laboratory at the university.

—Heidi Splette



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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.

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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.

Caution: 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, atropine-resistant bradycardia, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors. Cevimeline should be administered with caution to patients with a history of nephrotoxicosis or cholelithiasis. Contractions of the gallbladder or biliary smooth muscle could precipitate complications such as cholelithiasis or cholelithiasis 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		Adverse Event	Cevimeline 30 mg (tid) n=533		Placebo (tid) n=164	
	n	%	n	%		n	%	n	%
Excessive Sweating	18.7%	2.4%	1.8%	0.9%	Urinary Frequency	0.9%	1.8%	0.0%	0.0%
Nausea	13.8%	7.9%	1.2%	0.5%	Asthenia	0.5%	0.0%	0.0%	0.0%
Rhinitis	5.2%	5.4%	0.6%	1.1%	Flushing	0.3%	0.6%	0.0%	0.0%
Diarrhea	10.3%	10.3%	0.0%	0.1%	Polyuria	0.1%	0.6%	0.0%	0.0%
Excessive Salivation	2.2%	0.6%	0.0%	0.0%					

*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 30 mg (tid) n=533		Placebo (tid) n=164		Adverse Event	Cevimeline 30 mg (tid) n=533		Placebo (tid) n=164	
	n	%	n	%		n	%	n	%
Headache	14.4%	20.1%	14.2%	4.3%	Conjunctivitis	4.1%	3.6%	0.0%	7.3%
Sinusitis	12.3%	10.9%	0.0%	4.1%	Dizziness	4.1%	1.2%	0.0%	1.2%
Upper Respiratory Tract Infection	11.4%	9.1%	0.0%	3.7%	Fatigue	3.3%	1.8%	0.0%	3.0%
Dyspepsia	7.8%	8.5%	0.0%	3.3%	Surgical Intervention	3.3%	3.0%	0.0%	3.0%
Abdominal Pain	7.8%	5.4%	0.0%	2.3%	Insomnia	2.3%	1.8%	0.0%	1.2%
Urinary Tract Infection	6.1%	3.0%	0.0%	3.3%	Pain	3.3%	3.0%	0.0%	1.8%
Coughing	6.1%	3.0%	0.0%	2.8%	Skeletal Pain	2.8%	1.8%	0.0%	1.2%
Pharyngitis	5.2%	2.4%	0.0%	2.4%	Headache	2.4%	1.2%	0.0%	1.2%
Vomiting	4.6%	2.4%	0.0%	2.4%	Rigors	1.3%	1.2%	0.0%	1.2%
Injury	4.5%	2.4%	0.0%	1.3%	Anxiety	1.3%	1.2%	0.0%	1.2%
Back Pain	4.5%	2.4%	0.0%	1.3%					
Rash	4.3%	6.0%	0.0%	1.3%					

*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, hypotension, infection, fungal infection, sinusitis, 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, fibrosis, infection, 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, hematoema, 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, 1 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, thrombocytopenia, 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, hyperlipidemia, hypertriglyceridemia, hyperuricemia, hypoglycemia, hypokalemia, hypomagnesemia, 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, dysphasia, dyslexia, dysphonia, agitated multiple sclerosis, involuntary muscle contractions, neuralgia, neuropathy, paresthesia, speech disorder, agitation, confusion, depression, 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, sicca, fungal infection, 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 chlamydia 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, dyspareunia, endometrial 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:

cholinergic syndrome, blood pressure fluctuation, cardiomegaly, postural hypotension, aphasia, convulsions, abnormal gait, hyperesthesia, paralysis, abnormal sexual function, enlarged abdomen, change in bowel habits, gum hypertasia, 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, anemia, apathy, delirium, delusion, dementia, illness, impotence, nervous, paranoid reaction, personality disorder, hyperthermia, glaucoma, alopecia, alopecia, 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 bronchoconstriction. It is not known if cevimeline is dialyzable.

DOSE 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
Manufactured by:
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References: 1. Data on file, Daichi Pharmaceutical Corporation, NDA #20-989. 2. File RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. Arch Intern Med. 2002;162:1293-1300. 3. Petrone D, Condemni JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum. 2002;46:748-754.



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