

Heart Benefits of Antimalarials in SLE Posited

BY TIMOTHY F. KIRN
Sacramento Bureau

SNOWMASS, COLO. — Antimalarials may not only treat active lupus, but also benefit the heart, W. Joseph McCune, M.D., said at a symposium sponsored by the American College of Rheumatology.

Lupus patients have an elevated risk of heart disease, and antimalarials have been shown to have a number of cardioprotective properties, said Dr. McCune, profes-

sor of internal medicine at the University of Michigan, Ann Arbor.

Such benefits may help offset the deleterious effects of prednisone, which has been shown to increase cholesterol levels. Each 10-mg titration in prednisone dosage is estimated to increase serum cholesterol by 7.5 mg/dL.

Several studies have shown that antimalarials are associated with lipid profile improvements in lupus patients. Each of those studies has treated patients some-

what differently and has shown slightly different results. "But the body of the studies clearly show that when a benefit is looked for, it is found mostly in lowering LDL cholesterol," Dr. McCune said.

In one study involving lupus patients not on corticosteroids, antimalarial therapy was associated with a 4% drop in total cholesterol at 3 months and a 1% drop at 6 months, compared with baseline levels. In patients on a corticosteroid, antimalarial therapy was associated with an

11% drop in total cholesterol at 3 months and a 9% drop at 6 months (J. Rheumatol. 1999;26:325-30).

Among diabetes patients, antimalarials have been shown to lower glucose levels in non-insulin-dependent patients. They also reduce insulin requirements in insulin-dependent patients. The dosages used have tended to be much higher than those typically used in rheumatology. However, even at the lower dosages used for treating lupus, it's believed that there is some positive effect on glucose tolerance, Dr. McCune said.

Dehydroepiandrosterone, which can be steroid sparing when it is added to lupus treatment, may produce increases in bone density that could offset steroid-induced osteopenia. But this has not been shown in patients with lupus, and the evidence is not definitive.

Statins clearly have immunomodulatory effects and have been shown to help prevent transplant rejection and to improve rheumatoid arthritis symptoms. However, at present there are no trials of statins used in patients with lupus, Dr. McCune said.



EVOXAC® Capsules
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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 CYP3A4/5 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	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 B1%: 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 abnormally, migraine, tooth disorder, epistaxis, flatulence, toothache, ulcerative stomatitis, anemia, hyposthesia, cystitis, leg cramps, abscess, enucleation, 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, thrombocythemia, 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, 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 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

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 bronchospasm. 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:
YAMANOUCHI PHARMA TECHNOLOGIES, INC., Norman, OK 73072

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References: 1. Data on file, Daiichi Pharmaceutical Corporation, NDA #20-989. 2. Fife 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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Biologic Doesn't Boost Remission Of Wegener's

Etanercept does not impact maintenance of remission in patients with Wegener's granulomatosis, according to results from a multicenter, randomized, placebo-controlled trial.

"Our results underscore three points," according to John H. Stone, M.D., of the Johns Hopkins Vasculitis Center, Baltimore. "Standard therapy fails to induce durable remissions in the majority of patients, etanercept does not enhance the effects of standard therapy, and even with the shorter courses of cyclophosphamide, now regarded as the standard of care, adverse events are common and frequently severe, with or without the addition of a specific tumor necrosis factor- α blockade."

Dr. Stone and other members of the Wegener's Granulomatosis Etanercept Trial Research Group evaluated etanercept for maintenance of remission in 180 patients with Wegener's granulomatosis (N. Engl. J. Med. 2005;352:351-61). Of the total, 89 received 25 mg etanercept twice a week via subcutaneous injection, and 91 received placebo. Each patient received standard therapy that consisted of glucocorticoids plus cyclophosphamide or methotrexate.

During the mean 27-month follow-up period, there were no differences between the etanercept group and the controls in terms of sustained remission (70% vs. 75%, respectively), sustained periods of low-level disease activity (87% vs. 91%, respectively), or the time required to achieve those measures.

In addition, 118 flares occurred in the etanercept group, compared with 134 in the control group, a difference that was not statistically significant.

—Doug Brunk