

Concomitant Golimumab Lessened Clinical RA

VITALS

Major Finding: RA patients who received methotrexate plus golimumab showed significantly better RAMRIS scores on MRI than did those who received MTX alone, as early as week 12 and continuing through week 24.

Data Source: A substudy of the GO-BEFORE study, involving 318 patients with active RA whose response to treatment was monitored via MRI.

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BY MARY ANN MOON
FROM ARTHRITIS & RHEUMATISM

Adding golimumab to methotrexate therapy lessened synovitis, osteitis, and bone erosion to a greater degree than did placebo plus methotrexate, a study has shown.

These improvements were evident as early as the 12th week of treatment on serial magnetic resonance imaging exams, which proved to be much more sensitive than conventional radiography at demonstrating the changes, said Dr. Mikkel Ostergaard, professor of rheumatology at Copenhagen University

Hospital at Glostrup, Denmark, and his associates.

They reported the results of a substudy of the 1-year GO-BEFORE (Golimumab Before Employing Methotrexate as the First-Line Option in the Treatment of Rheumatoid Arthritis of Early Onset) study, a large randomized controlled trial comparing various combinations of oral methotrexate (MTX), golimumab injections, and placebo in rheumatoid arthritis (RA) patients. GO-BEFORE’s findings demonstrated that after 28 weeks, “golimumab in combination with MTX reduced signs and symptoms and radiographic progression of RA in MTX-naive patients, with a safety profile similar to other anti-[tumor necrosis factor] agents,” the investigators said.

Their substudy involved 318 of these subjects who underwent serial MRI evaluations of the wrist and metacarpophalangeal joints at 12 and 24 weeks. Synovitis and osteitis (bone marrow edema), which signal heavy infiltration by inflammatory cells including osteoclasts, are precursors of new bone erosions. These changes are visible on MRI well before conventional radiography can detect them.

The MRIs were assessed by two readers and an adjudicator using the Rheumatoid Arthritis MRI Scoring (RAMRIS) system, “which has demonstrated very good reliability and a high level of sensitivity to change.” Study subjects who received MTX plus golimumab showed significantly better RAMRIS scores than did those who received MTX alone, as early as week 12 and continuing through week 24, Dr. Ostergaard and his colleagues said (Arthritis Rheum. 2011 Aug. 31 [doi 10.1002/art.30592]).

For example, at week 12, synovitis scores decreased by 1.92 points for the wrist and metacarpophalangeal joints and by 0.85 points for the wrist alone with combined therapy, compared with 0.14 points and 0.02 points with MTX alone. Bone edema–osteitis score decreased by 1.82 points with combined therapy but only by 0.56 points with MTX alone, and bone erosion scores decreased by 0.40 points vs. 0.24 points.

“Similar trends were observed in the sensitivity analyses conducted for the mean change in RAMRIS scores from baseline to week 24,” they added.

In a series of MRIs that were representative of the substudy population as a whole, “images show bone edema that was extensive at baseline, markedly decreased at week 12, and nearly resolved at week 24,” they noted.

The researchers emphasized that the substudy confirmed the conclusion of the entire GO-BEFORE clinical trial, but that MRI demonstrated the statistically significant difference between study groups in less than half the time (12 weeks rather than 28 weeks) and using fewer than half the subjects (318 patients rather than 637 patients). This documents that MRI is a more sensitive tool for detecting structural damage than conventional radiography, they said. ■

Brief Summary – See package insert for full Prescribing Information.

EVOXAC® Capsules
(cevimeline hydrochloride)

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 uterine 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 CYP3A3/4 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 carcinogenic 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
Excessive Sweating	18.7%	2.4%
Nausea	13.8%	7.9%
Rhinitis	11.2%	5.4%
Diarrhea	10.3%	10.3%
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.

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
Headache	14.4%	20.1%	Conjunctivitis	4.3%	3.6%
Sinusitis	12.3%	10.9%	Dizziness	4.1%	7.3%
Upper Respiratory Tract Infection	11.4%	9.1%	Bronchitis	4.1%	1.2%
Dyspepsia	7.8%	8.5%	Arthralgia	3.7%	1.8%
Abdominal Pain	7.8%	6.7%	Surgical Intervention	3.3%	3.0%
Urinary Tract Infection	6.1%	3.0%	Fatigue	3.3%	1.2%
Coughing	6.1%	3.0%	Pain	3.3%	3.0%
Pharyngitis	5.2%	5.4%	Skeletal Pain	2.8%	1.8%
Vomiting	4.6%	2.4%	Insomnia	2.4%	1.2%
Injury	4.5%	2.4%	Hot Flashes	2.4%	0.0%
Back Pain	4.5%	4.2%	Rigors	1.3%	1.2%
Rash	4.3%	6.0%	Anxiety	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, hyperostea, 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, hypoesthesia, cystitis, leg cramps, abscess, eructation, 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 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, hemorroids, 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 oxaloacetic 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 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, paroniria, somnolence, abnormal thinking, hyperkinesia, hallucination

Miscellaneous Disorders: fall, food poisoning, heat stroke, joint dislocation, post-operative hemorrhage
Resistance Mechanism Disorders: cellulitis, 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, bullous eruption, cold dammy 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, stranguy, 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, dementia, illusion, impotence, neurosis, paranoid reaction, personality disorder, hyperhemoglobinemia, apnea, atelectasis, yawning, oliguria, urinary retention, distended vein, lymphocytosis

The following adverse reaction has been identified during post-approval use of EVOXAC®. Because post-marketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Post-Marketing Adverse Events: Liver and Biliary System Disorders: cholecystitis

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.

Rx Only

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