

# OA Treatment Options Remain Disappointing

BY SALLY KOCH KUBETIN

EXPERT OPINION FROM A  
SEMINAR ON RHEUMATOLOGY

SANTA MONICA, CALIF. – Advances in biomarker research and imaging may eventually make earlier diagnosis of osteoarthritis a reality. Unfortunately, such technologies remain prohibitively expensive for routine use.

And there's another problem: nothing to offer patients by way of an effective early therapy for knee OA.

"So at the present time, when such treatments are not available, the benefit of early diagnosis is really to identify individuals at an early stage when an investigational therapy might be of use, and such individuals can be enrolled in clinical trials," Dr. Amanda E. Nelson noted.

"In the absence of specific disease-modifying treatments, the extra expense of an MRI for diagnosis is not warranted in daily practice at this time," advised Dr. Nelson of the University of North Carolina at Chapel Hill.

What has stymied the development of effective drugs for altering the course of knee OA?

The progress is slow for a few reasons, according to Dr. Nelson. Among them are lack of sensitive, cost-effective early diag-

nostics to best identify candidates for treatment, medicine's as-yet poor understanding of the causes of progression in OA, and its inability to identify which patients will progress to knee OA. This disease has a very long natural history: An injury in one's 20s may not lead to OA until after age 40 years. These things make trials difficult to conduct and to fund.

Current treatment is directed toward late-stage disease, and by and large these therapies focus on easing pain, not on modifying the course of the disease, Dr. Nelson said at a meeting sponsored by Skin Disease Education Foundation and the University of Louisville.

Corticosteroids have no effect on function, but they do relieve pain for 1-3 weeks. The administration of intra-articular hyaluronans eases pain and preserves or improves function for 5-13 weeks, judging from a systematic review (Cochrane Database Syst. Rev. 2006 [doi:10.1002/14651858.CD005328.pub2]).

On the investigational front, at least one phase III trial of the cyclooxygenase/lipoxygenase (COX/LOX) agent licofelone has been completed.

This investigational agent is an anti-inflammatory agent without the adverse effects of COX inhibition. Findings from a trial of 355 patients with knee OA showed that licofelone given in a 200-mg dose twice daily preserved the volume of knee cartilage as well as did naproxen given in a 500-mg dose twice daily, with

– CINODS protect the gastric mucosa and act as both a vasodilator and an inhibitor of platelet aggregation, thereby preventing vascular damage (J. Pharm. Pharm. Sci. 2008; Sep 20;11:81s-110s).

Findings from research using intra-articular injection of the cytokine inhibitor IL-1Ra in humans has been disappointing. The drug did not ease pain at 12 weeks but did provide more short-term pain relief.

Some investigators were keeping a close eye on trials of tanezumab, a monoclonal antibody against nerve growth factor that showed early efficacy in OA pain.

Although Pfizer Inc. has halted the trials because of increased progression and higher numbers of joint replacement, it is unclear whether that was related to the drug or to increased activity by the study subjects who experienced pain relief.

SDEF and RHEUMATOLOGY NEWS are owned by Elsevier. Dr. Nelson said that her funding sources include a National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases loan repayment grant and an American College of Rheumatology Research and Education Foundation Clinical Investigator Fellowship Award. She reported having no other disclosures. ■



A video interview with Dr. Amanda E. Nelson is available at <http://www.rheumatologynews.com/>.

less GI toxicity (Ann. Rheum. Dis. 2009;68:938-47).

Another category of symptomatic treatment that has gone through a phase III trial is COX-inhibiting nitric oxide donors (CINODs). These agents have anti-inflammatory properties similar to those of NSAIDs, but – unlike NSAIDs

## ACTEMRA® (tocilizumab)

In the all-exposure population, the rate of malignancies remained consistent (1.10 events per 100 patient-years) with the rate observed in the 6-month controlled period [see Warnings and Precautions].

### Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 mg/kg or 8 mg/kg ACTEMRA plus DMARD, and at least 1% greater than that observed in patients on placebo plus DMARD, are summarized in Table 2.

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 mg/kg or 8 mg/kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

Preferred Term	6-Month Phase III Controlled Study Population				
	ACTEMRA 8 mg/kg Monotherapy N = 288 (%)	Methotrexate N = 284 (%)	ACTEMRA 4 mg/kg + DMARDs N = 774 (%)	ACTEMRA 8 mg/kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

### DRUG INTERACTIONS

#### Other Drugs for Treatment of Rheumatoid Arthritis

Population pharmacokinetic analyses did not detect any effect of methotrexate, nonsteroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance.

Concomitant administration of a single dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists [see Dosage and Administration].

#### Interactions with CYP450 Substrates

In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, eg, oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

#### Live Vaccines

Live vaccines should not be given concurrently with ACTEMRA [see Warnings and Precautions].

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

**Teratogenic Effects. Pregnancy Category C.** There are no adequate and well-controlled studies in pregnant women. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg/kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphic effect at any dose, tocilizumab produced an increase in the incidence of

## ACTEMRA® (tocilizumab)

abortion/embryo-fetal death at 10 mg/kg and 50 mg/kg doses (1.25 and 6.25 times the human dose of 8 mg/kg every 4 weeks based on a mg/kg comparison).

### Nonteratogenic Effects.

Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

### Pregnancy Registry:

To monitor the outcomes of pregnant women exposed to ACTEMRA, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

### Nursing Mothers

It is not known whether tocilizumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

Safety and effectiveness of ACTEMRA in pediatric patients have not been established.

### Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. The frequency of serious infection among subjects treated with ACTEMRA 65 years of age and older was higher than those under the age of 65. As there is a higher incidence in infections in the elderly population in general, caution should be used when treating the elderly.

### Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology [see Warnings and Precautions].

### Renal Impairment

No dose adjustment is required in patients with mild renal impairment. ACTEMRA has not been studied in patients with moderate to severe renal impairment.

### OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported in which a patient with multiple myeloma received a dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg/kg, although all 5 patients at the highest dose of 28 mg/kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

### PATIENT COUNSELING INFORMATION

#### Patient Counseling

Patients should be advised of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

#### • Infections:

Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

#### • Gastrointestinal Perforation:

Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

Genentech USA, Inc., A Member of the Roche Group  
South San Francisco, California 94080-4990  
Copyright © 2010 Genentech USA, Inc. All rights reserved. 10627200

**Genentech**  
A Member of the Roche Group