

Tocilizumab Is Beneficial in Moderate to Severe RA

BY NANCY WALSH
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BARCELONA — In a multicenter double-blind study, treatment with the interleukin-6 signaling blocker tocilizumab not only significantly reduced disease activity among patients with rheumatoid arthritis but also improved physical function, fatigue, and quality of life.

A total of 622 patients with moderate to severe rheumatoid arthritis (RA) were ran-

domized to receive intravenous tocilizumab in doses of 4 mg/kg or 8 mg/kg every 4 weeks or placebo. They also received background methotrexate in doses of 10-25 mg/week and corticosteroids in doses of 10 mg/day or less, according to Dr. Rieke H.E. Alten of the Schlosspark Klinik, Berlin.

The patients' mean age was 51 years, and more than half were women. Their mean disease duration was 7.5 years, and they had taken a mean of 1.5 disease-modifying antirheumatic drugs before undertaking

the experimental regimen. All of them had swollen joint counts of six or more and tender joint counts of at least eight.

By week 24, a significantly greater proportion of patients treated with tocilizumab achieved an American College of Rheumatology (ACR) 20 response than did those who received placebo. In patients in the low-dose tocilizumab group, 13.5% achieved this level of response, as did 27.5% of those in the high-dose group. In those receiving placebo, 0.8% reached an

ACR20 level of response, Dr. Alten reported in a poster session at the annual European Congress of Rheumatology.

Tocilizumab treatment also resulted in a marked increase in the proportion of patients who achieved moderate or good response according to the criteria of the European League Against Rheumatism. A total of 61.9% and 79.5% of patients in the low- and high-dose groups, respectively, had moderate or good responses.

On the Health Assessment Questionnaire

Amitiza® (lubiprostone) Capsules

Initial U.S. Approval: 2006

BRIEF SUMMARY OF PRESCRIBING INFORMATION- Please see package insert for complete prescribing information.

1 INDICATIONS AND USAGE

Amitiza® is indicated for the treatment of chronic idiopathic constipation in adults.

2 DOSAGE AND ADMINISTRATION

The recommended dosage for Amitiza is 24 mcg taken twice daily orally with food. Physicians and patients should periodically assess the need for continued therapy.

3 DOSAGE FORMS AND STRENGTHS

Amitiza is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg of lubiprostone.

4 CONTRAINDICATIONS

Amitiza is contraindicated in patients with known mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

The safety of Amitiza in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with Amitiza and should be capable of complying with effective contraceptive measures. See *Use in Specific Populations* (8.1).

5.2 Nausea

Patients taking Amitiza may experience nausea. If this occurs, concomitant administration of food with Amitiza may reduce symptoms of nausea. See *Adverse Reactions* (6.1).

5.3 Diarrhea

Amitiza should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. Patients should be instructed to inform their physician if severe diarrhea occurs. See *Adverse Reactions* (6.1).

5.4 Bowel Obstruction

In patients with symptoms suggestive of mechanical gastrointestinal obstruction, the treating physician should perform a thorough evaluation to confirm the absence of such an obstruction prior to initiating therapy with Amitiza.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions in dose-finding, efficacy, and long-term clinical studies:

The data described below reflect exposure to Amitiza in 1175 patients (29 at 24 mcg once daily, 1113 at 24 mcg twice daily, and 33 at 24 mcg three times daily) over 3- or 4-week, 6-month, and 12-month treatment periods; and from 316 patients receiving placebo over short-term exposure (≤ 4 weeks). The total population (N = 1491) had a mean age of 49.7 (range 19-86) years; was 87.1% female; 84.8% Caucasian, 8.5% African American, 5.0% Hispanic, 0.9% Asian; and 15.5% elderly (≥ 65 years of age). Table 1 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza (any dosage) and that occurred more frequently with study drug than placebo. In addition, corresponding adverse reaction incidence rates in patients receiving Amitiza 24 mcg once daily and in patients receiving Amitiza 24 mcg twice daily are shown.

Table 1: Percent of Patients with Adverse Reactions in Clinical Studies of Amitiza

System/Adverse Reaction ¹	Placebo	Amitiza 24 mcg Once Daily	Amitiza 24 mcg Twice Daily	Amitiza Any Dosage ²
	N = 316 %	N = 29 %	N = 1113 %	N = 1175 %
Gastrointestinal disorders				
Nausea	3	17	29	29
Diarrhea	<1	7	12	12
Abdominal pain	3	3	8	8
Abdominal distension	2	—	6	6
Flatulence	2	3	6	5
Vomiting	—	—	3	3
Loose stools	—	—	3	3
Abdominal discomfort ³	—	3	2	2
Dyspepsia	<1	—	2	2
Dry mouth	<1	—	1	1
Stomach discomfort	<1	—	1	1
Nervous system disorders				
Headache	5	3	11	11
Dizziness	<1	3	3	3
General disorders and site administration conditions				
Edema	<1	—	3	3
Fatigue	<1	—	2	2
Chest discomfort/pain	—	3	2	2
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	—	3	2	2

¹ Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).

² Includes patients dosed at 24 mcg once daily, 24 mcg twice daily, and 24 mcg three times daily.

³ This term combines "abdominal tenderness," "abdominal rigidity," "gastrointestinal discomfort," and "abdominal discomfort."

Nausea: Approximately 29% of patients who received Amitiza (any dosage) experienced an adverse reaction of nausea; 3% of patients had severe nausea while 8% of patients discontinued treatment due to nausea. The rate of nausea associated with Amitiza (any dosage) was substantially lower among male (7%) and elderly patients (18%). Further analysis of the safety data revealed that long-term exposure to Amitiza does not appear to place patients at an elevated risk for experiencing nausea. The incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea reported at the 24 mcg once daily dosage (17%). In open-labeled, long-term studies, patients were allowed to adjust the dosage of Amitiza down to 24 mcg once daily from 24 mcg twice daily if experiencing nausea. Nausea decreased when Amitiza was administered with food. No patients in the clinical studies were hospitalized due to nausea.

Diarrhea: Approximately 12% of patients who received Amitiza (any dosage) experienced an adverse reaction of diarrhea; 3% of patients had severe diarrhea while 2% of patients discontinued treatment due to diarrhea.

Electrolytes: No serious adverse reactions of electrolyte imbalance were reported in clinical studies, and no clinically significant changes were seen in serum electrolyte levels in patients receiving Amitiza.

Less common adverse reactions: The following list of adverse reactions includes those that occurred in less than 1% of patients receiving Amitiza (any dosage) in dose-finding, efficacy, and long-term clinical studies and that were considered by the investigator to be probably or definitely related to treatment with study drug. Moreover, the list includes only those events that occurred in at least two patients and more frequently in patients receiving Amitiza than those receiving placebo.

Gastrointestinal disorders: fecal incontinence, defecation urgency, frequent bowel movements, intestinal functional disorder, constipation, eructation
Musculoskeletal and connective tissue disorders: muscle cramp, joint swelling, myalgia

Nervous system disorders: dysgeusia, syncope, tremor

Respiratory, thoracic, and mediastinal disorders: pharyngolaryngeal pain, cough

Skin and subcutaneous tissue disorders: hyperhidrosis, cold sweat
General disorders and administration site conditions: influenza, pain

Metabolism and nutrition disorders: decreased appetite

Psychiatric disorders: anxiety

Disability Index (HAQ-DI), clinically relevant improvements were seen in patients in both tocilizumab groups, starting at week 4, and with greater mean reductions than the protocol-defined minimally clinically difference of -0.25.

In patients in the tocilizumab 4-mg/kg and 8-mg/kg groups, 64.8% and 63.1%, respectively, had a 20% or greater improvement in HAQ-DI, compared with 47.5% of the placebo patients.

All treatment groups showed improvements in the physical and mental components of the Short

Form-36 Health Survey. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale scores also improved in all treatment groups, but greater mean changes were consistently observed for patients in the tocilizumab groups, he wrote.

Moreover, the FACIT fatigue score increased by a clinically meaningful four points or more from baseline by week 4 in both tocilizumab groups.

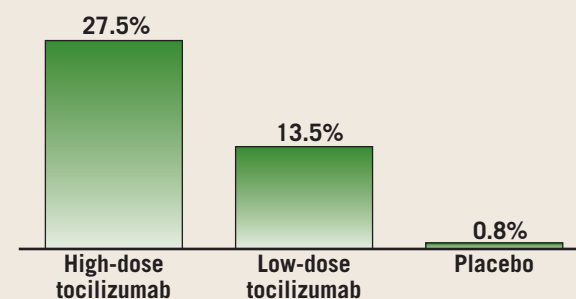
RA is associated with functional disability, limitation of daily activities, and decreased quality of life.

Fatigue is a particular problem, with more than 40% of patients reporting clinically important levels of fatigue, Dr. Alten noted.

The rationale for targeting IL-6 in RA lies in observations that this cytokine appears to play a role in the damage to periarticular bone and cartilage. It also activates T cells, B cells, and macrophages and is a central mediator of the hepatic acute phase response (Lancet 2007; [doi:10.1016/S0140-6736(07)60784-3]).

The study was sponsored by Hoffmann-La Roche Inc. ■

Patients With Moderate to Severe Rheumatoid Arthritis Achieving an ACR20 Response



Note: Based on a randomized 24-week study of 622 patients.
Source: Dr. Alten

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6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Amitiza. Because these 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.

Voluntary reports of adverse reactions occurring with the use of Amitiza include the following: syncope, malaise, increased heart rate, muscle cramps or muscle spasms, rash, and asthenia.

7 DRUG INTERACTIONS

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug-drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to the metabolite M3 (See *Pharmacokinetics, Metabolism* [12.3]). Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone. No additional drug-drug interaction studies have been performed. Based on the available information, no protein binding-mediated drug interactions of clinical significance are anticipated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C. [See *Warnings and Precautions* (5.1).]

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats or rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the recommended human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of Amitiza at 24 mcg twice daily, four women became pregnant. Per protocol, Amitiza was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been studied.

8.5 Geriatric Use

The efficacy of Amitiza in the elderly (≥ 65 years of age) subpopulation was consistent with the efficacy in the overall study population. Of the total number of constipated patients treated in the dose-finding, efficacy, and long-term studies of Amitiza, 15.5% were ≥ 65 years of age, and 4.2% were ≥ 75 years of age. Elderly patients taking Amitiza (any dosage) experienced a lower incidence rate of associated nausea compared to the overall study population taking Amitiza (18% vs. 29%, respectively).

8.6 Renal Impairment

Amitiza has not been studied in patients who have renal impairment.

8.7 Hepatic Impairment

Amitiza has not been studied in patients who have hepatic impairment.

10 OVERDOSAGE

There have been two confirmed reports of overdosage with Amitiza. The first report involved a 3-year-old child who accidentally ingested 7 or 8 capsules of 24 mcg of Amitiza and fully recovered. The second report was a study patient who self-administered a total of 96 mcg of Amitiza per day for 8 days. The patient experienced no adverse reactions during this time. Additionally, in a Phase 1 cardiac repolarization study, 38 of 51

patients given a single oral dose of 144 mcg of Amitiza (6 times the recommended dose) experienced an adverse event that was at least possibly related to the study drug. Adverse reactions that occurred in at least 1% of these patients included the following: nausea (45%), diarrhea (35%), vomiting (27%), dizziness (14%), headache (12%), abdominal pain (8%), flushing/hot flash (8%), retching (8%), dyspnea (4%), pallor (4%), stomach discomfort (4%), anorexia (2%), asthenia (2%), chest discomfort (2%), dry mouth (2%), hyperhidrosis (2%), and syncope (2%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Amitiza is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg of lubiprostone. Amitiza is available as follows:

- Bottles of 100 (NDC 64764-240-10)
- Bottles of 60 (NDC 64764-240-60)

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F).

PROTECT FROM EXTREME TEMPERATURES.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing Instructions

Patients should take a single 24 mcg capsule of Amitiza twice daily with food or a meal. The capsule should be taken once in the morning and once in the evening daily as prescribed. Physicians and patients should periodically assess the need for continued treatment with Amitiza.

17.2 Nausea and Diarrhea

Patients should take Amitiza with food or a meal to reduce symptoms of nausea. Patients on treatment who experience severe nausea or diarrhea should inform their physician.

Marketed by:

Sucampo Pharmaceuticals, Inc., Bethesda, MD 20814
and

Takeda Pharmaceuticals America, Inc., Deerfield, IL 60015

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Long-Term Steroids in RA May Cut Function

BARCELONA — Rheumatoid arthritis patients who use corticosteroids frequently over the long term can maintain a low disease activity state but suffer deterioration of their functional capability, Dr. Eiichi Tanaka reported at a poster session at the annual European Congress of Rheumatology.

"A low disease activity state caused by corticosteroid use may not represent a 'true' low disease activity state," noted Dr. Tanaka of Tokyo Women's Medical University, and his associates.

The investigators followed 224 RA patients with a low disease activity state during 2000-2005.

The patients had a mean age of 56 years and a mean disease duration of about 8 years, and were enrolled in the study for at least 3 years.

Every 6 months, the investigators collected measurements on the Disease Activity Score-28 (DAS-28) and Japanese version of the Health Assessment Questionnaire (J-HAQ).

DAS-28 scores did not change substantially over the course of the study in 135 patients who never used corticosteroids, 33 who used steroids an average of less than 9 months per year, and 56 who took steroids an average of more than 9 months per year.

No patient had a DAS-28 greater than 3.2 at each assessment.

But long-term functional capacity, as measured by the J-HAQ, declined in the heavy corticosteroid users, improved slightly among moderate corticosteroid users, and improved the most in patients who did not use corticosteroids.

The use of corticosteroids was the most significant factor contributing to the final J-HAQ score, after the adjustment of a multiple linear regression analysis for age, gender, disease duration, initial J-HAQ score, and seasonal effects.

A little more than 90% of the patients in each group used disease-modifying antirheumatic drugs during the study.

"Along with the achievement of a low disease activity state, long-term efficacy, long-term functional prognosis, and the quality of remission also need to be considered in the strict control of RA activity," Dr. Tanaka and his colleagues concluded.

—Jeff Evans