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.

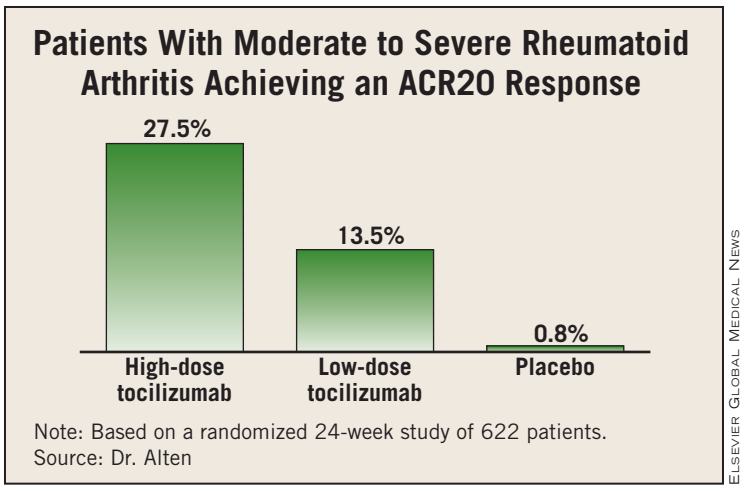
All treatment groups showed improvements in the physical and mental components of the Short Form–36 Health Survey. Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale scores also improved in all treatment groups, but greater mean changes were consistently observed for patients in the 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. ■



6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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