

Folic Acid May Limit Methotrexate's Efficacy in RA

BY CHRISTINE KILGORE
Contributing Writer

Use of concomitant folic acid significantly reduced the efficacy of methotrexate and did not decrease the overall incidence of symptomatic adverse events, according to the findings of a post hoc analysis.

The two phase III, randomized, controlled trials included in the analysis—one conducted in the United States and the

other in Europe—compared the effects of 52 weeks of daily leflunomide with weekly methotrexate (MTX) in patients with active rheumatoid arthritis.

Although measuring the effect of folic acid was not the primary objective, the trials provided a look at its effect, because almost all of the patients in the MTX arm of the U.S. study—98%—were given daily folic acid, yet only 10% of the patients receiving MTX in the multinational European study received folate, each of them

after they experienced an adverse event.

Previously published articles on the trials reported that 52% of patients in the MTX arm of the U.S. study achieved an American College of Rheumatology (ACR) 20 improvement response, compared with 65% of patients in the European trial.

Investigators of the new post hoc analysis set out to adjust for significant differences in the baseline characteristics of patients that made comparisons at 52

weeks “difficult to interpret,” explained Dinesh Khanna, M.D., of the University of Cincinnati and the Veterans Affairs Medical Center.

Using propensity score matching methods to adjust for these baseline differences, they found that folic acid use reduced the probability of an ACR 20 response by 15%-21%, or an average of 17%, in 225 patients who received the treatment compared with 443 patients who did not (Arthritis Rheum. 2005; 52:3030-38).

The results were consistent when comparing ACR 50 and ACR 70 improvement responses, the investigators said.

When they stratified patients by the presence or absence of rheumatoid factor,

Use of the supplement reduced the probability of an ACR 20 response by 17%, in 225 patients, compared with 443 patients who did not receive it.

they found a statistical trend toward a lower ACR 20 response rate in the RF-negative group taking folic acid compared with the RF-positive group taking folic acid—a finding that “may suggest a preferential response to MTX

in patients with active RA based on their RF status,” they said.

Adverse events were reported in 93% of patients in the U.S. study and 94% in the European study.

As expected, patients receiving prophylactic therapy with folic acid had a lower incidence of liver function abnormalities. Elevated levels of alanine aminotransferase and aspartate aminotransferase were seen in 30% and 20%, respectively, of the patients in the U.S. study and in 63% and 47% of the patients in the European study.

But, “surprisingly,” patients in the U.S. study also had a higher incidence of symptomatic side effects (76%, vs. 68%), including a higher incidence of diarrhea, headache, and oral ulcers, compared with the European study group, the investigators reported.

The U.S. study involved 482 patients, 179 of whom received MTX and had RF data available. The European study involved 999 patients, 489 of whom received MTX and had RF data available.

The newly reported post hoc analysis combined all patients from both studies who were taking folic acid (50 from the European study, 175 from the U.S. study), as well as those who were not taking folic acid (439 in Europe and 4 in the U.S.).

Patients who did not receive folic acid had a significantly lower mean body weight, a shorter mean duration of RA, and higher mean disease activity, as well as higher scores on the HAQ disability index and the Disease Activity Score in 28 joints (DAS28).

The mean dosage of MTX at 52 weeks was similar in the two trials, and oral folic acid was generally given in both studies at a dosage of 1-2 mg/day.

Treatment of osteoporosis Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX[®] (alendronate sodium) 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either FOSAMAX or placebo are presented in the following table.

	Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients			
	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX [*] % (n=196)	Placebo % (n=397)	FOSAMAX** % (n=3236)	Placebo % (n=3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.5	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

*10 mg/day for three years

**5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B1% of patients in either treatment group are presented in the following table.

	Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients			
	Once Weekly FOSAMAX		FOSAMAX	
	70 mg % (n=519)	10 mg/day % (n=370)		
Gastrointestinal				
abdominal pain	3.7	3.0		
dyspepsia	4.1	2.7		
acid regurgitation	1.9	2.4		
nausea	1.9	2.4		
abdominal distention	1.0	1.4		
constipation	0.8	1.6		
flatulence	0.4	1.6		
gastritis	0.2	1.1		
gastric ulcer	0.0	1.1		
Musculoskeletal				
musculoskeletal (bone, muscle, joint) pain	2.9	3.2		
muscle cramp	0.2	1.1		

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B2% of patients treated with either FOSAMAX or placebo are presented in the following table.

	Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients			
	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Other studies with FOSAMAX[®] (alendronate sodium)

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

	Osteoporosis Prevention Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients			
	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	Once Weekly FOSAMAX 35 mg % (n=361)	Once Weekly FOSAMAX 5 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

	One-Year Studies in Glucocorticoid-Treated Patients Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients		
	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
	Gastrointestinal		
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melenia	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to A2.0 mg/dL (0.65 mM) were similar in both treatment groups.

In a fifteen week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 70 mg.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use with alendronate:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, INFORMATION FOR PATIENTS, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, Dental).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain).

Skin: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

For more detailed information, please read the Prescribing Information.

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