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, 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.

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.

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. ■