



## PIC QUESTION OF THE WEEK: 05/25/05

Q: What are the recommendations for folate supplementation in patients treated with methotrexate (MTX) for rheumatoid arthritis?

A: MTX continues to be one of the most important disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis. Although biologic response modifiers such as etanercept and infliximab have become increasingly popular, many patients with the disease still use MTX itself or in combination with the TNF- $\alpha$  inhibitors. Low-dose MTX produces a number of adverse reactions including stomatitis, anorexia, nausea, diarrhea, increased aminotransferase (especially ALT) levels, bone marrow suppression, pneumonitis, and hepatic fibrosis. For several years, folate supplementation has been considered beneficial in reducing the frequency of many adverse effects due to low-dose MTX. Recent, large-scale trials of folate supplementation conclude that it does decrease ALT values and improves continuation rates by reducing the incidence of liver function test abnormalities and gastrointestinal intolerance. There is still some debate whether supplementation significantly decreases the frequency of gastrointestinal effects caused by MTX. Folate supplementation also appears to decrease plasma homocysteine levels and may consequently reduce the risk of cardiovascular disease in rheumatoid arthritis patients treated with MTX. Both folic acid and folinic acid have been used to supplement low-dose MTX. Most authors now suggest that folic acid is preferable because of its cost and ease of administration. Folate supplements do not appear to reduce the efficacy of MTX, although a somewhat higher dose of MTX may be necessary to maintain the same therapeutic effect. Dosage of folic acid has been highly variable. Many authors recommend 1 to 4 mg daily while a dose of 7 mg once weekly is also cited. Others suggest a minimum of 400 mcg daily is sufficient to reduce common complications of MTX. A recent review of the topic recommends that 5 mg of folic acid be given on the morning following the day MTX is administered. Although the optimal dosage of folate has not been resolved, supplementation appears to provide sufficient benefit to be routinely used in combination with low-dose MTX.

### References:

- Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology* 2004;43:267-71.
- Van Ede AE, Laan RF, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis. *Arthritis Rheum* 2001;44:1515-24.

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