Benefits of folic vs folinic acid addition in rheumatoid arthritis being treated with methotrexate alone

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Title: Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis.

Aim
Methotrexate (MTX) is a folate antagonist, disease-modifying anti-rheumatic drug (DMARD) widely employed in rheumatoid arthritis (RA). When administered as a single drug, MTX is associated with adverse effects in 30% of cases, side effects that could be partially counteracted by simultaneous folate supplementation. A 48-week, randomized, double-blind, prospective, placebo-controlled trial was carried out to evaluate and compare the benefits of folic versus (vs) folinic acid administration in patients (pts) affected by RA, during therapy with MTX.

Methods
411 pts with RA diagnosed on the basis of the American College of Rheumatology (ACR) criteria were consecutively recruited. Pts were ≥ 18 years old. Pts having a minimum Disease Activity Score (DAS) of 3.0 were selected. Corticosteroids or nonsteroidal anti-inflammatory drugs were allowed if they had been taken at a constant dosage for at least one month before the trial. Previous MTX treatment, other DMARDS if administered ≤ 2 weeks before the trial, concomitant folic or folinic therapy, anti-folic antibiotics, allopurinol, pregnancy, breast-feeding, inadequate contraception, ≥ 20 alcoholic drinks/week, elevated transaminase, creatinine clearance < 50 ml/min, WBC < 3.5 x 10^9/liter, or a platelet count < 120 x 10^9/liter were exclusion criteria. Enrolled pts were randomly divided into 3 groups. The treatment protocols were: Group 1 - MTX plus placebo (137 pts); Group 2 - MTX plus folic acid at a dosage of 1 mg/day every morning (133 pts); and Group 3 - MTX plus folinic acid (2.5 mg/week) 24 hours after MTX administration (141 pts). Evaluation by the study observers was standardized by appropriate training. For each pt the same observer performed an initial evaluation and a check-up every 3 weeks. DAS was evaluated every 6 weeks. If necessary, the initial MTX dosage (7.5 mg/week) was allowed to be increased by 2.5 mg up to 25 mg/week. MTX toxicity was graded as mild, moderate or severe based on self-reports by the pts. Fries standard toxicity form, and standard laboratory investigations. In cases of adverse effects, the MTX dosage could be decreased by 2.5 mg/week before a choice was made to interrupt therapy. The percentage of drop-outs, established on the basis of severe or persisting/recurring moderate toxic effects, were the primary end point of the study.

Results
DAS did not differ between the three groups before or during trial. Only 5% of pts did not manifest an adverse effect. The percentage of adverse events which induced pts to discontinue MTX treatment were 38% in placebo group, 17% in the folic acid group, and 12% in the folinic acid group, with statistically significant differences between group 1 versus (vs) groups 2 and 3 (P < 0.001, in both comparisons), and no difference between groups 2 and 3. Excepting hepatotoxicity, no other adverse effects showed statistically significant differences in comparisons between the three groups. ALT values were elevated in group 1 vs groups 2 and 3 (P < 0.001). Alanine aminotransferase (ALT) assessment did not show a statistically significant difference in group 2 vs 3 (P = 0.32). Occasionally higher ALT values were found in 16.8% of pts from group 1, in 3.8% from group 2, and in 6.0% from group 3. Alcohol intake had no influence. An increased MTX dosage was necessary more often in the folate substitution groups than in the placebo group. Groups 2 and 3 showed an equivalent requirement for increased MTX dosages.

Conclusions
This work clearly demonstrates that the addition of folate, either folic or folinic acid, has an equivalent beneficial on ALT levels, but no impact on any other adverse effects in RA pts being treated with MTX. Folic acid is less expensive and easier to administer than folinic acid. Supplementation with folinic acid is of great help in preventing the hepatic adverse effects of MTX in pts affected with RA.

Related references
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Comment
Methotrexate had become the primary disease modifying anti-rheumatic drug (DMARD) for treatment of rheumatoid arthritis (RA) in the United States by the mid-1980s. Further more, the practice of adding folate supplementation became a common practice among US rheumatologists, based in large part on references cited from 1990 and earlier (1-3). In Europe, methotrexate and folate supplementation were not adopted at that time. Differences between US and European practices in the mid-1990s were seen in clinical trials which compared leflunomide to methotrexate, in which folate was taken by 98% of methotrexate-using patients in the US (4) versus fewer than 10% in Europe (5). Such differences were thought to explain the finding that 52% of patients in a US study met the American College of Rheumatology 20% response criteria (ACR 20), compared to 65% in a similar multi-national non-US trial (p < 0.05), as folate reduced the efficacy of methotrexate (6). However, differences in trial design and duration of disease may explain these obser vations (7).

Nonetheless, the withdrawal rate of less than 17% in the folic acid group and 12% in the folinic acid group, compared to 38% in patients who had no folate, indicates strongly that folate is effective to reduce methotrexate withdrawal. Similar changes were seen in DAS scores in the three groups, although the final methotrexate dose was 2.9 - 3.5 mg per week higher in patients who took folate.

Finally, it is of interest to note that the ACR20 responses seen in this study in patients who took methotrexate only (and not a new DMARD or biological agent) were in the range of 50-60% after 48 weeks. In studies of “step up” combination therapy of methotrexate with new DMARDs, ACR 20 re sponses after 24-30 weeks were seen in 46% of patients who took methotrexate with leflunomide, 48% with cyclosporine, 53% with infliximab and 71% with etanercept (8). Of course, studies of combination therapy were performed in patients with only partial clinical responses to methotrexate, and the data must be interpreted in that light. Nonetheless, the findings strongly suggest that methotrexate may be as effective a therapy in many patients with RA as new therapies, as suggested in several head-to-head comparisons (4, 9). This phenomenon may deserve further studies by the rheumatology community, as there currently is little commercial interest in clinical trials of methotrexate therapy.

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References

(This EBR was prepared with the assistance of Dr Luca Bertinotti, Fellow in Rheumatology)