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THE USE OF FOLATES CONCOMITANTLY WITH LOW-DOSE PULSE METHOTREXATE

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Over the past 15 years, methotrexate therapy for rheumatic diseases has evolved from a role as treatment for "intractable" inflammatory polyarthritis, to frequently the first choice of slow-acting remittive agents in early rheumatoid arthritis (RA). As rheumatologists have gained more experience with methotrexate, they have come to appreciate its quick and effective anti-inflammatory properties relative to alternative agents and the low incidence of serious toxicity. As a result, its uses have widened to other inflammatory rheumatic and nonrheumatic conditions, often in a role as a corticosteroid-sparing agent.

Experimentation, largely by dermatologists, led to the low-dose, weekly, oral or intramuscular methotrexate therapy now used for rheumatic diseases. It has been shown that titrating the dose of methotrexate between 5 mg and 20 mg weekly is associated with increasing anti-inflammatory activity.[6, 38] Experiments with higher-dose regimens have suggested efficacy of methotrexate where standard therapy has failed.[7, 39, 40] Unfortunately, higher doses of methotrexate also result in a higher frequency and severity of adverse events.[6, 46]

Despite the low frequency of serious toxicity with the standard regimen, there exist several side effects that limit methotrexate's use in certain patients or result in unwanted interruptions of therapy or a failure to titrate the dose optimally. For the most part, these adverse effects are the result of methotrexate's antifolate properties (e.g., hematologic, mucositic, and hepatic complications; alopecia). Oncologic proto-

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cols using extremely high doses of intravenous methotrexate (≤10 g) are well tolerated because of the concomitant use of folinic acid (leucovorin, citrovorum factor).[2, 14] In addition, repetitive high doses of folinic acid have been used to reverse serious acute methotrexate toxicity.[2, 14, 20] These observations have led to the evaluation of various folate regimens to reduce the frequency or dampen the severity of adverse events associated with the low-dose weekly methotrexate therapy for rheumatic diseases.

Essentially, there are two choices of agent to be used potentially as a folate supplement concomitantly with methotrexate: folic acid and folinic acid. Both have been evaluated in clinical trials and are used anecdotally in various ways. For folic acid to be effective, it must be able to compete with methotrexate as a substrate for dihydrofolate reductase so that it will be properly reduced to the biologically active form of folate necessary in the one carbon metabolism required in biosynthesis of certain amino acids (serine, methionine), de novo purine synthesis, and thymidine. In contrast, folinic acid (calcium 5-formyltetrahydrofolate) is a pharmaceutically synthesized, relatively stable, fully reduced form of folate developed to treat and prevent toxicity related to methotrexate therapy. Because it is fully reduced, it bypasses the inhibition of dihydrofolate reductase by methotrexate.[2, 14, 20] Given that it is synthetic and does not have as wide a use as folate in the general population, the cost per pill of folinic acid when compared to folate is substantial.

THE USE OF FOLIC ACID SUPPLEMENTS WITH METHOTREXATE

Although given the oncologic experience, folinic acid would be the logical choice as supplemental therapy when methotrexate is used in the rheumatic patient, there have been proponents of folate for several reasons. First, concern has existed that folinic acid would build up in polyglutamated stores of intracellular folate and lead to methotrexate resistance. Indeed, concerns have even existed regarding acute resistance as well. Second, there has been concern that there exists an enormous cost difference between folic acid therapy and folinic acid therapy. Finally, it has been argued by the same advocates of folic acid that it is safer and more convenient.[26]

At this time, there has been no clinical trial comparing folic acid versus folinic acid in this setting. Differences in study designs render meta-analyses unreliable. There have been no cost–benefit analyses to justify a recommendation that any given folate regimen be used at the inception of methotrexate therapy in all patients. There have been studies showing effectiveness of both folic acid and folinic acid in reducing side effects related to low-dose weekly methotrexate therapy.

The first successful placebo-controlled study was reported by Morgan and colleagues using 1 mg of folic acid daily.[24] Based on a toxicity

score developed by these investigators but never formally validated, they demonstrated that the folic acid supplementation was associated with lower toxicity scores and did not seem to interfere with the anti-inflammatory effects of methotrexate. Most importantly, this study did confirm that those with preexisting folate deficiency were more likely to experience methotrexate toxicity, and during therapy the mean corpuscular volume (MCV) tended to rise in the placebo group. There were no differences between groups in the complete blood count or serum liver function tests, however. This study had a number of flaws. First, it was a small study (32 patients in total) and all of the difference between the two study groups could be accounted for by only four patients. Second, the methotrexate regimen did not reflect current use: A median of 7.5 mg of methotrexate was used, which is lower than the usual median (between 10 mg and 12 mg weekly) which subsequently tended to rise even higher.[8, 17, 49] This raises a question about the efficacy of 1 mg of folate daily with commonly used higher doses of methotrexate. The investigators used three doses of methotrexate weekly (q12hr) and not single-dose therapy (currently used). Finally, the study was only 6 months long, suffering perhaps from being too short in duration because the highest dose of methotrexate employed may have been achieved only a few weeks before the end of the study. Prior use of methotrexate was allowed, if not in the preceding 6 months, providing a potential for selection bias or influence on the types and frequency of side effects.

To further elucidate the value of folic acid supplementation, these same investigators conducted a second controlled trial, this time comparing placebo to 27.5 mg of folic acid weekly (5.5 mg daily for 5 days) and 5 mg of folic acid weekly (1 mg daily for 5 days).[26] No folic acid was given the day of methotrexate therapy or the day after, suggesting that the investigators were concerned with the potential of daily folic acid inducing methotrexate resistance. This latter point was not discussed, although the investigators once again raised concerns regarding the potential for folinic acid (leucovorin) to induce methotrexate resistance. All folate-containing vitamins were stopped at study entry.

This study included more patients and had better power statistics based on their toxicity score, however. In addition, it lasted 48 weeks, thus being long enough to allow for the development of side effects, achieve optimal disease control, and observe for methotrexate resistance. The study did show that folic acid at either dose was associated with lower toxicity scores without interfering with the anti-inflammatory benefits of methotrexate. The higher dose of folic acid was associated with more of a reduction in the toxicity score. Curiously, although there was a significant reduction in the frequency of side effects between placebo and the lower folic acid group, there was no statistically significant reduction between placebo and the higher dose of folic acid. In fact, the frequency of side effects in the higher folic acid group was higher than the lower folic acid group. The difference in toxicity scores between the two folic acid doses was accounted for by only two patients.

Other problems exist with this study.[43] First, the median dose of

methotrexate (8.5 mg versus 9.6 mg, placebo to high-dose folate, respectively) is still lower than the current use. Thus, it still is not known how this regimen would fare at higher doses of methotrexate. The study lacked in its design the adjusting of folic acid doses when methotrexate toxicities developed. As a result, also unknown is whether the addition of folic acid once toxicity occurs or an increase in folic acid when toxicity occurs would be effective. This needs to be emphasized because these investigators recommend increasing doses of folic acid to control or reverse side effects. In addition, no differences in blood counts or serum liver function tests were noted between groups. Finally, concern exists regarding how much folic acid was actually received by those in the two nonplacebo groups. The investigators initially intended to study placebo versus 5 mg versus 50 mg. It was discovered during the study that in fact the higher dose group was receiving a lower dose as the result of a manufacturing error. The study medications (placebo and folic acid) were prepared at the study center as identical capsules. The bioavailability of this preparation when compared dose per dose with commercially available folate supplements is therefore unknown.

Two further studies are noteworthy. The first is a retrospective study of 200 patients with RA.[44] All but two patients received about 7 mg of folic acid as a total weekly dose. These patients were followed for a mean of 41.5 months. The authors' primary conclusion was that an elevated MCV in this group was found in 21% and was not a significant predictor of hematologic or other side effects, with the exception of heartburn. Of note, the incidence of any side effect during the study was virtually universal, with moderate to severe side effects (severity score 2–4) occurring at some point in over 20% of their patients. When the patients were compared with their own historical controls not on folate, significant reductions in gastrointestinal symptoms, stomatitis, and elevated liver function tests were noted. Unfortunately, these historical controls were neither well defined nor adequately contrasted against the folate group with respect to clinical variables. Furthermore, the mean dose of methotrexate was low by today's standards (8.5 mg/wk).

The second study was also retrospective and examined a group of 158 patients with RA receiving methotrexate followed 24 hours later by 5 mg of folic acid. Patients were followed up to 4 years. On this therapy, side effects were common (60%) and caused cessation of therapy in 90% of the cases. Only 25% of patients ceased methotrexate at 2 years, however, and discontinuation seemed to plateau thereafter.[13] This folate regimen is intriguing in that all the folate was given as a single dose weekly, unlike the Morgan study, which spread the same dose of folate (5 mg) over 5 days.[24, 26] As with the Morgan study, administration of folate was delayed, suggesting the same concern by the investigators (i.e., that folate taken at the same time as methotrexate might interfere with anti-inflammatory effects).

Unfortunately, no study to date has determined whether 1 mg folic acid daily supplements are better than a simple multivitamin, containing

the recommended daily requirement of 400 μg folic acid. In the United States, 140 μg folic acid per 100 gm soon will be a nutritional supplement in all grains and cereals, providing a further source of this agent.

THE USE OF FOLINIC ACID (LEUCOVORIN) SUPPLEMENTS WITH METHOTREXATE

Anecdotal reports of the use of folinic acid with methotrexate date back almost 20 years.[5, 32, 50] These reports did not note significant negative effects of the addition of the folinic acid. A multitude of dosing schemes subsequently have been reported; unfortunately, most of these studies lacked scientific validity and did not evolve from the oncologic experience.

The first study evaluated the administration of 45 mg of folinic acid between 4 and 6 hours after methotrexate. This 4-week study involved only seven patients. The mean dose of methotrexate was 9.6 mg (7.5 mg–12.5 mg) or 20% of the folinic acid dose. Not surprisingly, all the benefits of methotrexate were abrogated by such a high dose of folinic acid following so closely after the administration of methotrexate.[45] A similar outcome occurred in another study that used 15 mg of folinic acid given 2 hours after a mean dose of 7.9 mg methotrexate.[15] No folic acid study has attempted to give such high doses of folate so soon after methotrexate to see whether it would also abrogate the benefits of methotrexate.

The first attempt to use a delayed folinic acid regimen in a clinical trial was performed by Hanrahan and Russell.[8] Patients taking a mean of 18 mg methotrexate, who were about to discontinue methotrexate because of side effects, were given 2 daily doses of 10 mg folinic acid beginning at least 3 days after the methotrexate. Of the 13 patients enrolled, 11 had nausea as the major side effect of methotrexate. This study was placebo controlled with a crossover design, having two 4-week study periods. The investigators did not see any negative effect on inflammation. In the other folinic acid studies already discussed, flares occurred by 4 weeks. Although there was considerable improvement of nausea in patients, folinic acid could not be distinguished from placebo.

There are several problems with this study. First, the study lacked a washout period, thus there could have been carryover effects of folinic acid into the placebo period of the study when folinic acid was given in the first period. Second, the administration of folinic acid at least 3 days after the administration of methotrexate could have been too long a delay, as it would be in the oncologic experience, which used folinic acid rescue preventively with high-dose intravenous methotrexate.[2, 12, 14] In addition, the sample size is too small and the study duration possibly too short to distinguish both positive and negative effects of the addition of folinic acid.

This author became interested in the use of folinic acid with low-dose weekly methotrexate while studying high-dose methotrexate (500

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