

Methotrexate Therapy in the Year 2000: Outstanding Questions

Based on a presentation by Michael E. Weinblatt, MD

Presentation Summary

Methotrexate (MTX) is the dominant drug worldwide in the therapy of rheumatoid arthritis (RA). Extensively studied over the past 20 years, it has been found to slow the rate of progression of erosion and joint narrowing in many studies. Methotrexate has the ability to reduce doses of background steroids and nonsteroidal anti-inflammatory drugs, and it also has been associated with maintenance of a long-term clinical response. As a result, it has become the anchor drug in almost every combination therapy regimen, as well as in trials

with biological response modifiers. To date, no drug has consistently outperformed MTX in a comparative trial. It is effective in patients with all types of inflammatory arthritis and is relatively inexpensive compared with some of the newer treatments. Further-more, clinical trials show no difference in response between patients with early rheumatoid arthritis and those with longstanding disease. In the United States, somewhere between 300,000 and 400,000 patients currently receive MTX, making it the most popular disease-modifying antirheumatic drug (DMARD) in the country.

“Methotrexate (MTX) is one of my favorite drugs,” declares Michael E. Weinblatt, MD, Professor of Medicine, Harvard Medical School and Brigham & Women’s Hospital, Boston, Massachusetts. “It is the dominant drug worldwide in the therapy of rheumatoid arthritis (RA),” he explained, adding that “as we move into the year 2000, I believe it will still be a dominant drug.”

Methotrexate has undergone an extensive development program over

the past 20 years, and there also have been 4 placebo-controlled trials¹⁻⁴ as well as studies that compared it with azathioprine,⁵ oral gold,⁶ intramuscular gold,⁷ cyclosporine,⁸ leflunomide,⁹ and lenercept.¹⁰ A large US trial that compares etanercept to MTX will be completed shortly.

Benefits of Therapy

In many studies, radiography has been used to show the slowed rate of progression of erosion and joint narrowing with MTX therapy.¹¹⁻¹³

Several years ago, Dr. Weinblatt's group reported that MTX had actually induced the healing of erosions in a small number of patients.¹¹ "When you look carefully at the trials," Dr. Weinblatt said, "there is an improvement in functional status in the newer studies,"^{9,14} observing that in the earlier trials, functional status measurements were not available. Methotrexate has the ability to reduce doses of background steroids and non-steroidal anti-inflammatory drugs, Dr. Weinblatt said, adding that it also has been associated with maintenance of a long-term clinical response.¹⁵⁻¹⁸

Dr. Weinblatt noted that rheumatologists often go through a revisionist period, in which they look at a new drug and say: "Isn't this spectacular? It improves signs and symptoms, function, and radiographic results." Dr. Weinblatt observed that "We tend to forget that some commercially available drugs do the same thing."

Role in Combination Therapy

Methotrexate has become the anchor drug in almost every combination therapy regimen. It has been used with gold, azathioprine, cyclosporine, sulfasalazine, hydroxychloroquine sulfate, and mycophenolate mofetil, as well as in triple therapy. It has been the anchor drug in trials that have biological response modifiers.

Much of the work has been done using MTX in combination with anti-tumor necrosis factor (TNF) therapy, including that with infliximab, lenercept, etanercept, and D2E7. There are also ongoing programs to study interleukin-10 with MTX and interleukin-1 receptor antagonist with MTX, Dr. Weinblatt said.

Results of Comparative Trials

According to Dr. Weinblatt, no drug to date has consistently outperformed MTX in a comparative trial. The next drug that is better than MTX in terms of efficacy and safety in a comparative study may well redefine the standard

of care as treatment moves forward, he predicted.

Methotrexate has been demonstrated to be superior to oral gold (auranofin),⁶ and it is equivalent to but probably better tolerated than intramuscular gold.⁷ Response rates for MTX compared with auranofin were 68% versus 29%, based on American College of Rheumatology (ACR) criteria. Radiographic evaluation showed that MTX was superior to both oral and intramuscular gold with regard to erosion and joint space narrowing.

In a large study, MTX was shown to be superior to azathioprine clinically and in radiographic evaluation of erosion and joint space narrowing.¹² In a large North American study that has been presented only as an abstract, MTX was found to be superior to cyclosporine A.⁸ In the control trial with lenercept, the p55 TNF receptor, MTX produced a bit more favorable results (50% versus 38% improvement).¹⁰

A US study comparing MTX with leflunomide demonstrated the equivalence of the 2 drugs with respect to clinical effect and functional status (46% versus 52% improvement for MTX versus leflunomide).⁹ Radiographically, MTX was also found to be equivalent to leflunomide.

Etanercept, the p75 TNF receptor, is being compared with MTX in a large US trial of patients with early-onset RA. One of the primary outcome measurements of that trial will be X-ray outcome.

Studies of Long-Term Use

Methotrexate has been studied longer than any other antirheumatic therapy. Prospective studies have lasted as long as 132 months. The 2 longest studies were done by Dr. Joel Kremer in Albany and by Dr. Weinblatt's group in Boston. In them, patients were monitored for 132 to 160 months (Table).^{16,17} Thirty percent of patients were still on the drug after 11 years of treatment. They experienced a sustained clinical response and were

able to reduce their use of background steroids. Very few patients dropped out in the long-term studies because of lack of efficacy.

"Methotrexate has the highest long-term retention rate of any disease-modifying antirheumatic drug (DMARD)," Dr. Weinblatt said.^{19,20} One reason for these high retention rates is that for the last decade there have been no new therapies." He noted that when Dr. Pincus' group evaluated 5 or 6 rheumatology practices around the country to examine their standard of treatment, they found that in general about 60% of patients were still on the drug at 5 years.¹⁹ "As a result, Dr. Weinblatt said, "rheumatologists have tended to keep patients on MTX, and I suspect that with new treatments, these rates will decrease."

Dosage Selection

Dr. Weinblatt noted that most North American rheumatologists tend to start MTX at a dosage of 7.5 to 10 mg per week to minimize the side effects, with the dosage titrated upward to 10 to 25 mg per week if the lower dose is not efficacious. There has been only one dose-response study involving MTX, which was done by Furst and associates in the early 1980s.²¹ Based on that study as well as an examination of the clinical trials, Dr. Weinblatt believes that the effective dose of MTX is 10 mg/m², which is about 18 mg per week. "As we talk about combination trials and dose issues," he said, "I think we should remember that you really need to get to the 10 mg/m² dose before you would call someone a methotrexate treatment failure."

Dr. Weinblatt noted that a comparative trial that does not require the MTX dose to be stabilized at 15 to 20 mg per week probably has an inappropriate design. "I think there are some significant flaws in some recent trials in which the dose of MTX has not been increased to that level," he said. "If patients do not meet ACR response criteria, unquestionably the dose should

be increased." As an example, Dr. Weinblatt said that if 40% of study patients are still at a dose of 7.5 mg per week and are not clinically improved, the trial design should be questioned, because it has a significant impact on the interpretation of the data.

According to Dr. Weinblatt, a valid criticism of some recent combination therapy studies is that patients who have received lower doses of MTX have been entered in trials without any attempt to increase those doses. An increase in the dose of MTX alone might have been effective in controlling disease in these patients without the need for combination therapy. In terms of solo therapy, Dr. Weinblatt said that the dose must be increased to try to achieve efficacy and that a switch from oral to subcutaneous administration might be helpful.

New Therapies for Rheumatoid Arthritis (RA)

Many of the studies of new therapies to date have involved patients receiving chronic MTX therapy. For example, in their study of cyclo-

Table. Results of 2 Long-Term Prospective Studies of Methotrexate

| Variable | Weinblatt et al ¹⁶ | Kremer ¹⁷ |
|--------------------------|-------------------------------|----------------------|
| No. of patients | 26 | 29 |
| Duration (mo) | 132 | 160 |
| Dosage (mg/wk) | 5.0-20 | 7.5-25.0 |
| Clinical response | | |
| Significant improvement | Yes | Yes |
| Reduction in steroid use | Yes | Yes |
| Remission* | Yes | No |
| Withdrawals | 16 (62%) | 19 (66%) |
| Toxicity scale | 3 | 5 |
| Lack of efficacy | 1 | 0 |

*Remission based on American Rheumatism Association criteria.
 Toxicity scale = withdrawals due to adverse reactions.
 Lack of efficacy = withdrawals due to lack of response

sporine, Tugwell and associates randomized patients with active disease who were receiving chronic MTX therapy to receive either cyclosporine or placebo.²² "That is the design that the Food and Drug Administration (FDA) approved for labeling with cyclosporine, as well as the design it approved for labeling with etanercept," Dr. Weinblatt said, adding that whether the new therapy is equivalent to combination therapy is a question that has not been addressed, either in the cyclosporine studies per se or in the etanercept trial.

According to Dr. Weinblatt, another question is whether treatment should be initiated with combination therapy, a situation different from that of adding a new treatment to chronic MTX therapy.

"From the rheumatologist's standpoint, these questions are relevant," Dr. Weinblatt said. "If you started somebody on 2 or 3 drugs immediately, would you get a better response than you would to either drug alone?" All the studies have by design been short-term trials, he noted, observing that "rheumatologists and their patients really want to know the long-term implications of treatment not simply whether an agent works in the short term."

Although there is a potential for toxicities associated with drugs in combination with MTX, to date these toxicities have not occurred. Important questions that should be studied include:

- Is there an increased risk of infection?
- Is there an increased risk of lymphoma?
- What are the effects of MTX on the liver?

Issues that center on the possibility of additional short-term toxicity, long-term risks, and requirements for additional monitoring also must be addressed, Dr. Weinblatt said.

Conclusion

"I believe that methotrexate currently is the gold standard for treatment of RA," Dr. Weinblatt said, noting its advantages:

- No drug to date has been shown to be better than MTX.
- It has been more thoroughly studied in clinical trials than any other agent for RA.
- It has the highest retention rate.
- It is effective in patients with all types of inflammatory arthritis.
- It is easy to dose.
- Clinical trials show no difference in response between patients with early RA and those with longstanding disease.
- Toxicity has been well described over more than 2 decades of use.
- Monitoring guidelines and standardized laboratory tests have been developed.
- Folic and folinic acid may be used to reduce toxicity.
- Methotrexate is relatively inexpensive compared with some of the newer treatments.

Somewhere between 300,000 and 400,000 US patients currently receive MTX, making it the most popular DMARD in the United States. Although the MTX package insert states that it is approved for use in "severe and active RA" (usually after a course of at least one DMARD), Dr. Weinblatt suspects that "severe RA" is no longer a criterion and that many rheumatologists, at least in North America, also use it as the first DMARD.

Dr. Weinblatt noted that MTX is not only used in RA but has widespread use in almost every inflammatory rheumatic disease as well as a variety of other chronic inflammatory illnesses.

The key question, Dr. Weinblatt said, is not whether MTX works; the question is: Will other drugs supplant its use in the future?

... DISCUSSION HIGHLIGHTS ...

Following Dr. Weinblatt's presentation, he responded to questions from the roundtable participants.

Question: When biological agents are introduced in the treatment of rheumatoid arthritis, they will probably be labeled as being for use when established treatment is not effective or appropriate. You say that methotrexate is the gold standard. How will the biological agent fit in with this "golden" treatment?

Dr. Weinblatt: That's a complicated question. Biological agents certainly look very promising with respect to efficacy. If they maintain their safety profile over time, they might supplant methotrexate, but I think it's going to be an evolution.

Comment: I think it's worth emphasizing that although methotrexate does a lot, it does not ordinarily put patients into the sort of remission we would like to see.

Dr. Weinblatt: That's why I mentioned that the retention rates are artificially inflated. In the last decade, we had limited choices of other therapies. Patients were maintained on methotrexate, even though their joint counts might have gone from 35 down to 20. Whereas we were somewhat pleased with this in 1988, it is not a feature we are particularly pleased with now. Methotrexate by no means stops the disease; remission is almost unheard of with that drug, and I think it's unheard of with most of our therapies.

Comment: I am concerned about your comment that the methotrexate dose has to be pushed, and that a trial is not effective unless people are using high doses of methotrexate when you add another drug in combination. In my clinic, about 20% of patients can't take more than 7.5 mg of methotrexate a

week. They get oral ulcers or they have unacceptable hair loss, even with folic acid, and so we treat them with prednisone and other drugs. Those people would seem to be very good candidates for combination therapy.

Biological agents certainly look very promising with respect to efficacy. If they maintain their safety profile over time, they might supplant methotrexate, but I think it's going to be an evolution.

—Michael E. Weinblatt, MD

Dr. Weinblatt: I agree. I wasn't referring to the patient who can't increase the dose because of nausea, stomatitis, headaches, and other adverse effects. The problem is, if you design a trial in which you don't increase the dose in someone who's not having a side effect, the question arises: Why should we add a new treatment in addition to methotrexate if the patient is only taking 7.5 mg per week and tolerating it? Why not push the dose of methotrexate first and see what the response is?

In the studies we have designed, we have an "escape clause." If you can't tolerate a dose between 10 and 15 mg per week, you can enter the studies at a lower dose.

Question: Why hasn't the package insert for methotrexate been revised to reflect that rheumatologists often prescribe methotrexate before the failure of treatment with another DMARD?

Dr. Weinblatt: I can't comment on the label description; that is an issue between the FDA and the sponsor.

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