METHOTREXATE IN RHEUMATOID ARTHRITIS: A QUARTER CENTURY OF DEVELOPMENT

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ABSTRACT

Methotrexate (MTX) is now the most popular drug worldwide for the treatment of rheumatoid arthritis. Low-dose, weekly MTX (10 to 25 mg/wk) used as either monotherapy or in combination with other drugs has a superior efficacy profile as defined in placebo-controlled trials and comparable efficacy to other drugs including anti-TNF therapy. At 1 year, one third of patients on MTX have no radiographic progression and even greater effects are seen when combined with targeted biological therapies. MTX is well tolerated; gastrointestinal toxicity is the most common toxicity with rarely bone marrow, lung, or liver toxicity. MTX therapy has been a major advance in the treatment of rheumatoid arthritis and is now the cornerstone of therapy.

INTRODUCTION

Over the past 25 years methotrexate (MTX) has become the standard of care in the treatment of adult rheumatoid arthritis. This article reviews the development of MTX and why it has become the most popular drug in the world for the treatment of adult rheumatoid arthritis (RA).

EARLY DEVELOPMENT

The history of MTX dates back to 1948 with the initial report by Sidney Farber and the successful use of aminopterin, an anti-folate in the treatment of childhood leukemia (1). This began the use of antimetabolites in the treatment of childhood leukemia. One of the effects observed with aminopterin was the interference of proliferation of

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connective tissue. This observation led to a study in 1951 by Gubner et al. in rheumatoid arthritis (2). They administered aminopterin to several patients with RA, psoriasis, and psoriatic arthritis. A rapid improvement in RA signs and symptoms occurred in six of seven patients who received aminopterin, but a return in disease activity followed drug discontinuation. It was noted that psoriasis cleared in a patient who had "rheumatoid arthritis and psoriasis." This led the authors to expand their study to include six patients with psoriatic arthritis, with good results. There was an improvement in skin and joint disease within several weeks of treatment; however, side effects were noted.

Because of difficulty in manufacturing aminopterin, the compound was modified to offer easier synthesis; this modified compound was methotrexate. In 1962, Black et al. from the NIH reported positive results with MTX in both RA and psoriatic arthritis (3). Over the next 10 years, the dermatology community extensively studied MTX in psoriasis. At the same time that aminopterin was being tried in psoriasis and RA, corticosteroids were reported to be a great value in the treatment of RA. In 1950, Phillip Hench et al. received the Noble Prize for their study of corticosteroids in RA. The rheumatology community was uninterested in looking at MTX in RA partly due to this enthusiasm of rheumatologists for corticosteroids and the concern about using an anti-cancer therapy for a "benign disease" such as RA.

In 1972, Rex Hoffmeister, a practicing rheumatologist from Spokane Washington, reported positive effects with intramuscular MTX at doses of 10 to 15 mg per week in 29 patients with RA (4). Eleven of the 29 patients had "major" clinical improvements and an additional 14 had "moderate" improvements in RA activity. These patients underwent treatment for up to 25 months. When the dose was decreased to below 10 mg per week or when MTX was discontinued, a flare of arthritis occurred in more than 80% of the patients. This successful report was published only as an abstract. In personal communication with Dr Hoffmeister I asked him why he never published this study. He commented that the response to his abstract at the National American Rheumatism Association meeting was so negative that he did not want to spend the time submitting a manuscript only to have it rejected. He noted that the rheumatology community was particularly hostile to using an anti-cancer drug in the treatment of RA. Dr Hoffmeister continued to use MTX and expanded his experience to 78 patients with a treatment follow-up as long as 15 years, which he published in 1983 (5). Fifty-eight percent of patients showed a "marked" improvement and 36% of these were thought to be in com-

plete remission on MTX. Inadequate response to therapy led to drug discontinuation in only 13% of his patients.

After Hoffmeister's report, several other community-based rheumatologists reported positive results during the next 5 years. Robert Willkens, a community-based rheumatologist from Seattle, Washington, reported an initial series of 32 patients (6) which he expanded to 67 patients who received MTX from 3 months to 10 years (7). He reported an overall improvement in more than 75% of patients using MTX doses that ranged from 7.5 to 15 mg per week.

Despite the enthusiasm reported in the open studies, placebo-controlled studies with MTX in RA where not performed until the mid-1980s. Based on conversations with both Drs Hoffmeister and Willkens and my personal experience with MTX, I developed a placebo-controlled study of MTX for patients with active RA. In 1982, I submitted this protocol to Lederle Laboratories, the manufacturer of MTX. I was initially informed that they had limited interest in studying MTX in RA; MTX was off-patent and was now generic. However, 1 year later, I was invited to attend a meeting in Pearl River, New York, to discuss with Lederle, my research proposal. For reasons that are still not clear, the medical group at Lederle had now become interested in MTX to treat RA. Three other investigators were also in attendance to discuss their studies. John Ward and Jim Williams from the University of Utah had submitted a second placebo-controlled trial and Joel Kremer from Albany Medical School submitted an open study to examine the effects of MTX on liver histology. Based on the psoriasis experience, there was significant concern about the hepatotoxicity of MTX. We were informed that Lederle was now interested in supporting research regarding use of MTX to treat RA and that they would provide drug, matching placebo, and financial support for our studies.

RANDOMIZED, PLACEBO-CONTROLLED TRIALS

In 1983, we initiated our randomized, placebo-controlled, 24-week crossover study of 35 patients with refractory RA (8). The initial MTX dose was 7.5 mg per week with an increase at 6 weeks to 15 mg per week. A clinical improvement was observed as early as 3 weeks after MTX initiation, more than 50% of the patients achieved a greater than 50% improvement in the joint tenderness index, and 39% achieved a similar improvement in the joint swelling index. At 12 weeks, the standard parameters of RA activity were significantly improved in the MTX-treated patients as compared to those patients who were randomized to receive placebo. In the second 12 weeks of the study, a flare

of disease activity occurred generally by 3 to 6 weeks in those patients who crossed from MTX to placebo. The drug was well tolerated and at study completion patients entered into a long-term extension study that extended more than 11 years.

The other pivotal study was an 18-week, placebo-controlled study directed by Jim Williams and an NIH-funded study network of 189 patients with active RA (9). Patients initially received MTX at 7.5 mg per week with dose escalation to 15 mg per week. Significant improvement in all efficacy parameters were observed with MTX; 32% of the patients had at least a 50% decrease in the joint tenderness index and 21% had a similar reduction in joint swelling index.

Based on the data from these two pivotal studies including our 35-patient study, the US Food and Drug Administration approved MTX as a therapy for RA in 1988.

Two other randomized trials were published during the same time with similar positive results (10, 11). All four of the studies noted significant improvement in standard parameters of RA activity with MTX doses that ranged from 7.5 mg to 25 mg per week given either orally or by intra-muscular injection. Clinical response was evident within 3 to 6 weeks, and a flare of arthritis activity was observed when patients where crossed from MTX to placebo.

LONG-TERM EXPERIENCE

After the placebo-controlled studies, the development program with MTX moved along two parallel lines; long-term, open studies and active, blinded comparator trials. Long-term prospective studies were of great value to establish the potential role of MTX in a chronic disease such as RA. Patients from our initial randomized trial entered into a long-term prospective trial experience which lasted 11 years (12–14). Our long-term experience was similar to that reported by Kremer who prospectively studied 29 patients over 132 months (15–17). Both studies reported sustained clinical response with the ability to reduce or stop prednisone therapy, with few serious adverse events. One of the exciting aspects of the development program of MTX was the worldwide interest of rheumatologists that occurred after the publication of the randomized, placebo-controlled trials. In a 191-patient study from France, the probability of maintaining MTX at 5 years was projected at 46% (18). In a study of 152 patients from the University of Alabama, the probability of maintaining MTX up to 6 years was projected to be 39% (19). Retention rates increased as physicians became more familiar with MTX and its side effects. In an Australian

study of 596 patients, the retention rate for MTX was projected at 5 years to be 62% (20). After completion of our 9-month randomized trial comparing MTX to auranofin (21), 123 patients enrolled in a 5-year prospective study (22). Sixty-four percent of the patients completed the 5-year study, and only 7% withdrew due to lack of efficacy. A significant sustained clinical response, improvement in functional status, and a reduction in sedimentation rate was observed. All of the long-term studies reported sustained clinical response with favorable retention rates. In fact, the retention rates with MTX were the highest of any other disease modifying therapy during that period. Pincus reported the experience from community-based rheumatologists in the United States and observed that the rate of MTX retention was twice that observed with other disease-modifying treatments (23).

ACTIVE COMPARATOR STUDIES

After completion of the placebo-controlled trials, head-to-head active comparator trials of MTX to other approved disease-modifying treatments were initiated. In a 48-week double-blind study of MTX versus azathioprine, MTX was superior in improving clinical disease activity and patients receiving MTX showed less radiographic progression than those who received azathioprine (24). Other studies compared MTX to what was then the standard of care—intramuscular gold. MTX was better tolerated with higher retention rates and similar favorable effects upon radiographic progression (25, 26). In a study of patients who were relatively treatment-naïve, 281 patients were randomized to either receive MTX or oral gold (auranofin) in a 36-week, double-blind study (21). In this study, MTX was more effective and less toxic than auranofin with less radiographic progression (27).

By the early 1990s, MTX was established as the standard of care for RA therapy. This was based on data generated from the placebo-controlled trials, active comparator studies to standard disease modifying therapy, and long-term prospective experience. MTX was noted to be clinically effective, to reduce the rate of radiographic progression, to improve functional status, and to have a reasonably good tolerability profile. The most common side effect was gastrointestinal intolerance such as nausea and rarely stomatitis or diarrhea. Other toxicities included post-treatment fatigue, headaches, dizziness, and rheumatoid nodule formation. Many of these adverse events could be reduced with the use of folic acid or folinic acid. Serious toxicities such as bone marrow suppression and lung or liver toxicities were fortunately very uncommon.

COMBINATION THERAPY

The next step involved combining MTX with other standard approved treatments. The concept of combining therapies was adapted from the successful oncology experience in leukemia and lymphoma. Several combination studies with MTX were performed with the most successful being those that combined MTX with cyclosporine (28) and MTX with hydroxychloroquine and sulfasalazine (29). In these studies, combination therapy was better than monotherapy. Negative combination studies were reported during this time, but several of these studies used lower or sub-therapeutic doses of MTX in the combination (30, 31).

BIOLOGIC THERAPIES AND MTX

The next major advance in RA therapy was the development of targeted biological therapies. By the mid-1990s, there was great enthusiasm for the use of drugs that blocked tumor necrosis factor α (TNF). As monotherapy, anti-TNF treatment was extremely effective. Studies comparing MTX to anti-TNF therapy were initiated in the late 1990s. The Early Rheumatoid Arthritis study was the first to directly compare an anti-TNF therapy to MTX (32). In this study of early RA, 632 patients were randomized to receive either etanercept (the p75 TNF soluble receptor) administered 25 mg twice a week as a subcutaneous injection, or oral MTX weekly up to 20 mg per week. During the first 6 months of the study, etanercept achieved a faster and better clinical response than MTX. This was not unexpected because monotherapy studies with etanercept reported clinical responses as soon as 2 weeks after drug initiation. What was surprising was that after 6 months there was no significant clinical difference observed between the patients receiving MTX versus those receiving the anti-TNF therapy. However, etanercept had a much better effect on radiographic progression than that observed with MTX.

Several studies in which MTX was compared to anti-TNF therapy alone and the combination of anti-TNF plus MTX confirmed that MTX as monotherapy was very similar in clinical effect to that observed with anti-TNF therapy (33, 34). These combination studies also showed that the combination of MTX plus anti-TNF therapy was significantly better than monotherapy with MTX or monotherapy with anti-TNF therapy. All of the combination studies with anti-TNF therapy plus MTX showed an approximate 10- to 15-point greater improvement with the combination treatment as compared to monotherapy. In fact, many of the biologics currently used with MTX show this additive effect when

the biologic is combined with MTX. These observations have only increased the use of MTX in the treatment of RA.

Because of the cost issues involved regarding use of biological therapies, most rheumatologists now initiate treatment with MTX as the first-line therapy for RA. For patients who do not have a dramatic response to the MTX, a biologic is added to the background MTX. Approximately one third of patients will have a remarkable response with MTX and will not require the addition of a biological therapy.

The role of MTX in the treatment of RA has now been well established. It has become the standard of care and first-line therapy for patients who have RA. In patients who have an incomplete response on MTX, other drugs are combined with MTX to improve clinical response. MTX has changed the lives of patients with RA!

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DISCUSSION

Dover, Baltimore: I am absolutely stunned by your historical perspective because apparently the reluctance to use any cancer drug is a very common phenomenon. I had something to do with the introduction of 5-azacytidine and hydroxyurea in sickle cell disease. In that case, a Nobel laureate wrote an editorial in *The Lancet* about how one should never use any cancer drugs in non-cancerous diseases and then your final comments, I think, are quite remarkable also in that the drugs we are now using in sickle cell disease, hydroxyurea, we don't know how it works either and that's been now 20 years.

Weinblatt, Boston: So let me just tell you that when I submitted my abstract of our study to our national organization, it was accepted and it was accepted as a poster for the last session of the day, which meant no one was there and I was placed next to a closet; and 2 weeks after that, we had an acceptance from the *New England Journal of Medicine*, which I think really jumpstarted it. The validation from the journal really helped actually the development of this molecule.

Hellman, Baltimore: Mike, thanks for a nice presentation and, more importantly, thanks for your work, which has improved the lives of so many of the patients with rheumatoid arthritis. The question I wanted to ask is: tapering the methotrexate, given the graph that you have, if someone is doing well, do you leave them on it forever?

Weinblatt, Boston: So the question regards tapering of the molecule. My own bias is that most patients are going to need to be on some dose of methotrexate forever but our studies, as well as studies by Joel Kremer in Albany, have demonstrated that you can actually reduce the dose of the drug over time. In fact, he did a study where he went to every other week therapy, which I traditionally do in in my patients. This drug has a long biological half-life and in patients that are in remission, you certainly can reduce the dose. It's almost like the same as using prednisone in polymyalgia rheumatica. Dose reduction and if there is a flare, dose escalation. So, some of my patients may be on a dose as low as 2.5 mg every other week actually to control their disease.

Crowley, Boston: A historical footnote and a question. The same thing that happened here with methotrexate happened to Robert Schwartz when he began to use it in lupus and autoimmune diseases. He was pilloried, publically, for the use of azathioprine and methotrexate in diseases which have become standards of care for the non-cancer use. So it's interesting to see the follow-up on it. The question relates to the length of time and the number of people in the follow-up. Given that you now have sufficient numbers and particularly over durations, I am sure you have thought of this, about doing genome-wide association studies on the responders versus the non-responders to pick the profile earlier. You usually typically need large numbers of both and in most

diseases, you can't acquire that unless you do it over a number of years, but it strikes me that when you are getting into registries and things like that, you have the opportunity to do that and most of these patients would be very grateful. I'm thinking specifically of the HIV-resistant and responders where they map it very specifically to genes and actually to a specific binding site. It strikes me that this is a field ready to do that and I'm sure you are on it, but I'd like to know if you have support for that and et cetera.

Weinblatt, Boston: So there have been a number of studies that have actually looked at that question. Many of the studies have been underpowered. We've looked at our own registry at The Brigham, which is about 1300 patients which have been typed and there are some selective SNPs (single nucleotide polymorphisms) in the folate pathway that actually predict response and there are some that identify patients that have some adverse events but that's not been replicated. The issue that we have is how we define response and I think one of the critical aspects as we in rheumatology move forward, we need to be more defined about the patient responder versus the non-responder but there are a number of centers around the world now that are collecting the data to help address that further.

Lang, San Antonio: Mike, great presentation. As you alluded to, there is an NIH study ongoing enrolling 7000 patients using methotrexate to prevent cardiovascular disease and stroke. That is obviously new territory for cardiologists, prescribing an anti-cancer drug. Give us some insight whether 20 mg weekly will actually produce a result and what sort of side effects we should be looking for.

Weinblatt, Boston: Paul, actually, I think is going to comment about that in his presentation. Having assisted Paul in the development of the protocol, we know that 20 mg a week of methotrexate in clinical trials has a significant impact upon acute phase reactants. CRP studies have been done and MTX doses between 15 and 20 mg per week have a remarkable effect on reduction in CRP generally within a week of starting treatment. So if the goal is to reduce inflammation burden, then I think 20 mg per week will do it. In rheumatoid arthritis, the top therapeutic dose is about 25 mg per week. For the cardiology community, we aren't excited about pushing to that level. I think it is going to be hard enough to get the cardiologists just to be interested in studying this drug anyway because of the historical aspects of it but 20 mg per week in rheumatology settings has been extremely well-tolerated and has a remarkable impact upon inflammation.

Gershon, New York: Lovely presentation. I have two questions. I wonder if this medication is used in children with rheumatoid arthritis and the other one pertains to would you tell us something about infections that you see as side effects.

Weinblatt, Boston: So with regard to children, the drug actually is a standard of care in juvenile idiopathic arthritis. It is actually the first therapy that pediatric rheumatologists go to in children with polyarticular disease. It has been well-validated in international trials. Children require slightly higher doses than adults, interestingly enough, for control of their disease and it is the first line therapy in children. The only infection that is statistically higher in the control group has been viral infections, particularly zoster, there have been slightly higher rates with zoster. We do see opportunistic infections rarely including Pneumocystis and fungal disease but it is very rare, we see the usual rates of bacterial and viral infections and with slightly higher rates with zoster.

Gershon, New York: Thank you.