Clinical trials to establish methotrexate as a therapy for rheumatoid arthritis

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ABSTRACT

The development of methotrexate (MTX) as a therapy for rheumatoid arthritis (RA) evolved initially from positive case reports, uncontrolled case series and then several decades later placebo controlled studies followed by active comparator studies. These studies established MTX as a major therapy for RA. The importance of MTX in the treatment paradigm has only been enhanced over the past decade by the increased efficacy observed when small molecules and biologics are added to MTX. Since the first randomised studies were performed in the 1980s, MTX has now become the most well-studied disease modifying therapy to date and the most popular drug worldwide in the treatment of RA. This chapter will review the history of the development of MTX in RA.

Investigators in the 1940s noted the importance of folic acid and its derivatives in haematopoietic function. Additional preclinical studies suggested that anti-folate therapy could be effective in the treatment of certain malignancies. This led to the development of antifolate compounds in the treatment of malignancy, in particular childhood leukaemia. Based on the observation that aminopterin, an antifolate agent, was a potent inhibitor of connective tissue proliferation, Gubner and associates administered this drug to seven patients with RA in 1951 (1). A rapid improvement in arthritis symptoms occurred in six of the seven patients, but exacerbations followed drug discontinuation. The value of folic acid antagonists in psoriasis was observed when psoriasis cleared in a patient given aminopterin for RA, leading the authors to expand the study to include six patients with psoriatic arthritis with good effectiveness (1). Modifications of the aminopterin structure to allow for easier production led to the synthesis of MTX. O’Brien in 1962 reported the positive effect of MTX in RA and psoriatic arthritis (2). Whereas dermatologists subsequently studied and prescribed MTX for many years for the treatment of psoriasis, there was limited interest in this drug in the rheumatology community. The reason for this disinterest in the rheumatology community is not known, but part of it might be ascribed to the great enthusiasm for corticosteroids during that time frame.

Subsequent reports of the effect of MTX in RA were limited until 1972 when Hoffmeister reported a beneficial response with intramuscular MTX at dosages of 10 to 15 mg per week in 29 patients with RA (3). A major clinical improvement occurred in 11 and a moderate improvement in 14 patients during a mean observation period of 25 months. A decrease in dose below 10 mg per week or discontinuation of therapy produced deterioration in 22 of the 29 patients. Hoffmeister expanded his open series to include 78 patients with treatment follow-up as long as 15 years (4). Forty-five patients (58%) showed a “marked” improvement; 28 (36%) of these were felt to be in “complete remission”. An inadequate initial treatment response led to drug discontinuation in ten patients. In four patients, despite an initial beneficial response, the arthritis activity recurred and MTX was discontinued.

Following Hoffmeister’s first report, several open studies primarily from community-based rheumatologists were reported in the early 1980s. In a 3-month open study of 6 patients, significant improvement in the number of involved joints, grip strength, and duration of morning stiffness was noted with no significant toxicity (5). Willkens reported an initial series of 32 patients and two years later he expanded the series to 67 patients who received oral...
MTX at dosages that ranged from 7.5 to 15mg per week with an observation period of 3 months to 10 years (6, 7). An improved global response occurred in 76% of the patients with a significant decrease in active joints and erythrocyte sedimentation rate (ESR). Thirty-four patients discontinued therapy, including 11 because of lack of efficacy. Significant improvement was also reported in a 21-patient open study of 38 weeks duration in which MTX was administered by either an oral or an intramuscular route, with dosages that ranged from 7.5mg to 25mg per week (8). In a follow-up of these 18 patients, a sustained clinical response was observed after a mean of 42 months of treatment (9). In another open study, intravenous MTX at dosages as high as 50mg per week was effective in 11 of 14 patients, with improvement occurring within 4 weeks of drug initiation (10). Twenty-eight patients with refractory RA were treated with low dose oral MTX (7.5mg weekly) over 2 years and nineteen of 28 (67%) had a positive overall response, while 7 (25%) patients showed a sufficient improvement to continue therapy (11). In an open study combining intramuscular gold with MTX there was a suggestion of efficacy without unusual toxicity (12). A comparison of these open studies published in the late 1970s and early 1980s is difficult because of varying definitions of clinical efficacy and different dosing regimens. However, all of them reported substantial short-term benefit with low-dose weekly MTX in active RA. Due to the enthusiasm generated by these uncontrolled studies, four placebo-controlled trials in patients who had active disease despite prior disease-modifying therapy, including gold salts, were performed. The largest randomised trial was an 18-week multicenter study of 189 patients on low-dose (7.5-15.0mg) weekly oral MTX (13). A significant improvement in all efficacy variables and ESR was reported with MTX. Individual patient response, defined as a 50 percent decrease in the joint pain/tenderness index, was noted in 32 percent and a similar reduction in the swelling index occurred in 21 percent of the patients receiving MTX.

A similar significant improvement in clinical variables was reported in a 35-patient, 24-week, double-blind crossover trial of low-dose (7.5 to 15.0mg) weekly MTX (14). Clinical improvement began as early as 3 weeks after MTX initiation. Individual patient response defined as greater than 50 percent improvement in the joint pain/tenderness index or joint swelling index occurred in 54 percent and 39 percent, respectively, of the MTX patients. In this study a flare of disease activity was observed in patients who crossed from MTX to placebo. These two studies were the pivotal studies submitted by the manufacturer of MTX to support approval of low dose MTX for RA. MTX was approved by the United States Food and Drug Administration in 1988 as a therapy for RA. Two other randomised trials, including a six-week double-blind parallel study of 48 patients (15) and a 26-week crossover study of 12 patients (16) also noted similar improvement with MTX therapy. These four randomised trials, even though of different duration, design, and with different dosing regimens and outcome measures, confirmed the short-term efficacy of MTX in refractory RA. Clinical response was evident within three to six weeks at doses that ranged from 7.5 to 25mg/week by either oral or intramuscular injection. An integrated analysis of the four randomised trials noted a significant improvement with MTX in all variables except the 50-foot walk time (17). An analysis of patient benefit expressed as percentage of reduction/improvement from baseline over and above that attributable to placebo revealed the following with MTX: 46 percent reduction in duration of morning stiffness, 37 percent reduction in joint pain/tenderness and swelling indexes, 27 percent reduction in number of painful joints, 26 percent reduction in number of swollen joints, 26 percent improvement in patient and physician assessment, and 15 percent reduction in the ESR. A flare of disease activity was observed in the short-term crossover studies within a month of cessation of therapy (14, 16). Two long-term studies (18, 19) also reported a flare of arthritis activity following MTX discontinuation. In one of these long-term studies, 12 patients who had been treated for a mean of 22 months and had either a "good" or "excellent" response on MTX were randomised to receive MTX or placebo for 3 months (18). A significant deterioration in arthritis activity occurred in all seven patients randomised to placebo, including a worsening in the number of painful and tender joints, duration of morning stiffness, global assessment of disease activity, and ESR. Following the positive results of MTX in the placebo-controlled studies in patients with RA, MTX was compared with other disease-modifying antirheumatic drugs (DMARDs). In a 24-week double-blind study of 42 patients, MTX was compared to azathioprine (20). The MTX-treated group exhibited a trend toward more rapid and marked improvement. Radiological evidence of progressive joint damage was similar in both treatment groups. No difference in efficacy was noted between the two drugs, but a type II statistical error attributable to a small population size may have been present. No significant difference in efficacy between these two treatments was also observed in a comparative randomised trial with 53 patients with RA (21). However, after one year, more than half of the patients in both groups had discontinued therapy due to inefficacy or adverse events. In a 249-patient, 48-week, double-blind, prospective, controlled trial of MTX, azathioprine or the combination of both therapies, 45% of the patients in the MTX-only group had at least 30% improvement in at least three of four variables, compared with 38% and 26% in the combination and azathioprine-only groups, respectively (22). A trend toward decreased radiologic progression was seen in the MTX-treated patients. In another 48-week double-blind, randomised trial, the number of withdrawals caused by adverse effects was significantly higher among patients receiving azathioprine than MTX, and efficacy was better in the MTX group (23). The authors concluded that MTX was superior to azathioprine in treating
RA. Patients treated with MTX showed significantly less radiologic progression than patients treated with azathioprine (24). In three double-blind controlled studies comparing MTX and gold sodium thiomolate (GSTM), no significant differences in effectiveness and in the progression of radiographic evidence of erosion were seen, but MTX was better tolerated (25-27). Menninger reported a three-year study comparing MTX and GSTM in 174 patients with erosive RA and withdrawal because of toxicity was significantly higher in the GSTM group (28). Rau et al. reported that both MTX and GSTM reduced the slope of radiographic progression during three years of follow-up. There was some advantage of parenteral gold, but there was no significant intergroup difference (29). In a double-blind study comparing weekly MTX and daily auranofin, MTX was found to be not only more effective, but also less toxic than auranofin over a 36-week period (30). These studies comparing MTX and other older DMARDs showed that MTX had one of the best efficacy/toxicity ratios.

The next step in the development program of MTX addressed questions about long term response, function, quality of life and radiographic progression. Long-term observations in three initial open trials noted a sustained clinical response with MTX (4, 6, 9). Despite an increase in arthritis activity that was noted in one report in 10 of 23 patients after 16 months of treatment (31), there appears to be a very positive clinical response and favourable retention rate with MTX in all of the other long-term trials. Kremer and Lee prospectively studied 29 patients, and a sustained improvement in arthritis activity was reported after 29 months (32), 53 months (33), and 90 months of treatment (34), although the number of tender joints worsened in the interval between 53 months and 90 months. After 90 months, 21 of 29 patients (72%) continued to take MTX and only 2 patients (7%) withdrew because of lack of efficacy. Similarly, in the long-term prospective extension of a randomised crossover trial (14), a sustained clinical effect was observed after 36 (35), 84 (36), and 132 months (37) of MTX therapy. A significant reduction in prednisone dose was achieved without a flare in arthritis activity. Of 26 patients enrolled in the long-term extension study, 10 patients completed the trial and received a total of 11 years of MTX therapy. Although adverse events were frequent throughout the study, withdrawals due to MTX toxicity occurred in 12% of patients, and only one patient discontinued treatment after 18 months because of lack of efficacy.

Of great importance in the long-term studies was the fact that many patients were able to continue MTX therapy for prolonged intervals. Other studies have also reported favourable retention rate with MTX. In another study, 25 of 45 patients (56%) continued the drug for 176 weeks, and no withdrawals were due to lack of response (38). Similarly, after completion of a 9-month randomised trial comparing MTX to auranofin (30), 123 patients were enrolled in a 5-year multicentre, prospective study of oral MTX (39). A sustained clinical response and a significant improvement in ESR and functional assessment scores were reported. Thirty-six per cent of the patients withdrew from the study, and only 7% withdrew due to lack of efficacy. Sany et al. reported a 191-patient open, prospective study (40). The mean duration of MTX therapy was 19±13.2 months (range 3–58). As in the other studies, significant improvement in all clinical variables and reduction in steroid dose were observed. The probability of maintaining MTX at 5 years was projected at 46% and 6% of the patients withdrew from the study due to lack of efficacy. In a study of 152 patients from a single academic centre, the probability of continuing to take MTX at year 6 was predicted at 39%, with the major reason for dropout being drug toxicity (41). Interestingly, whereas only 40% of the patients in this study who began MTX treatment prior to 1984 continued the treatment for 3 years, 60% of those who began after 1984 remained on the drug regimen after 3 years. The authors suggested that the improvement in the percentage of patients able to continue MTX resulted from the fact that “physicians became more familiar with the drug and its side effects”. In another study of 124 patients treated with MTX, 52% withdrew from MTX in the first 2 years, the most common reason again being adverse drug reactions (42). In 2 studies from Australia, similar favourable retention rates were observed. In one study of 587 patients the termination rate after 70 months was 24%, with the most common reason for termination being drug toxicity (43). Similarly, a study of 596 patients maintained by community-based rheumatologists in Australia projected that, at 5 years, 62% of the patients would continue MTX (44). This is similar to data reported by Pincus et al. of community-based rheumatology practices in the United States, in which the rate of MTX continuation was double that seen with other second line therapies (45). All of these studies suggested that the major reason for discontinuation of MTX was more likely to be toxicity, rather than lack of efficacy.

Thus, before the discovery of biological agents, MTX represented the first revolution in the treatment of RA. Currently, it is one of the most effective and commonly used DMARDs to treat RA, and it is internationally accepted as the first choice in the management of RA. The use and interest in MTX as a therapy for RA has only increased with the observations that when MTX is added to biologics the response rates are much higher than for the biologics by themselves. MTX has become the most well studied therapy in the treatment of RA and serves as the cornerstone of therapy.

References
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