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EFFICACY OF METHOTREXATE IN RHEUMATOID ARTHRITIS

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SUMMARY

Methotrexate (MTX), an antifolate agent, has been used in the treatment of rheumatoid arthritis (RA) for over two decades. Open clinical studies and short-term, randomized, placebo-controlled studies demonstrate the efficacy of MTX in active RA. Long-term prospective studies, including two of over 7 yr duration, report a sustained response and a corticosteroid-sparing effect. Comparative studies demonstrate superior efficacy to auranofin, azathioprine and cyclosporin A. A highly favourable retention rate with the drug has been noted in large studies from academic and community-based practices. Radiographic studies suggest a slowing of radiographic progression with the compound. MTX has become an accepted and widely used treatment for active RA.

KEY WORDS: Methotrexate, Rheumatoid arthritis, Antifolate, Comparative study.

AMINOPTERIN, a folic acid antagonist and parent compound of methotrexate (MTX), was initially developed for the treatment of acute childhood leukaemia. The use of folic acid antagonists followed the isolation of folic acid from the liver in 1943. The molecular formula of folic acid, and two methods for its synthesis, were described in 1946. It was appreciated that folic acid was important in haematological function, and this led to a series of experiments with folic acid in the treatment of leukaemia and solid tumours. Administration of folic acid to patients with chronic myeloid leukaemia resulted in haematological and clinical relapse. In one patient, an improvement was associated with the withdrawal of folic acid, and in another patient, a haematological response occurred when the patient was started on a diet low in folic acid. In 1948, Farber *et al.* [1] reported their classic study on the use of aminopterin in the treatment of childhood leukaemia. This study established the role of folic acid antagonists in the therapy of malignancy.

In 1951, Gubner *et al.* [2] reported an open study of aminopterin in patients with psoriasis, rheumatoid arthritis (RA) and psoriatic arthritis. Refinement of the aminopterin compound led to the development of MTX. MTX was extensively studied as a therapy for psoriasis in the 1960s. Weinstein and Frost [3] developed an oral regimen in which MTX was administered at 12-h intervals in three doses, once a week. This dosing regimen was based on the difference between the maturation time of psoriatic skin *vs* normal skin. This weekly cycled regimen produced less toxicity than daily therapy and was as good as single, larger dose, parenteral injections. A natural progression with MTX was from the treatment of psoriasis to psoriatic arthritis. In 1964, Black *et al.* [4] reported a double-blind study of MTX *vs* placebo in patients with active psoriatic arthritis. An improvement in both the psoriasis and arthritis occurred in the treatment group. Responses were detectable within a few weeks of drug initiation. In 1984, Willkens *et al.* [5] reported a double-blind study with MTX at a maximum dose of 15 mg/week. In this small study of psoriatic arthritis, MTX was no better than placebo at improving joint swelling or joint tenderness. MTX was superior to placebo, however, in the physician assessment of arthritis activity and in improving the amount of psoriatic skin surface area. The lack of greater improvement in this particular study may have been due to the low dose of MTX utilized and the small sample size.

RHEUMATOID ARTHRITIS: OPEN STUDIES

Following the observation that MTX was of value in psoriatic arthritis, in 1972, Hoffmeister [6] reported beneficial effects with i.m. MTX in 29 patients with RA. The dose of MTX was 10–15 mg/week. Over the next 15 yr, several open studies confirmed Hoffmeister's initial observations of the beneficial effects of low-dose, weekly treatment with MTX in active RA. Willkens and Watson [7] reported their experience with low-dose oral MTX in 67 patients with RA who had failed gold therapy. A one-step response was observed in 33 patients (49%) and a two-step response was observed in 18 (27%) of the patients. The duration of therapy was from 3 months to 10 yr and the dose of MTX ranged from 7.5 to 22.5 mg/week.

Hoffmeister [8] expanded his initial series to include 78 patients with a treatment duration as long as 15 yr. Forty-five of his patients (58%) were observed to have had a marked improvement, with 28% judged to be in complete remission. The dose of MTX ranged from 10.0 to 15.0 mg/week.

Steinsson *et al.* [9] observed a significant improvement in an open study, involving 21 patients, with a mean treatment duration of 38 weeks. The dose of MTX ranged from 7.5 to 25.0 mg/week given either orally or by i.m. injection. Fifty-two per cent of the patients were noted to be responders. A follow-up report of 18 of these patients noted a sustained clinical response after a mean of 42 months of treatment [10].

Michaels *et al.* [11] reported the use of i.v. MTX in 14 patients at a dose as high as 50.0 mg/week, with a

duration of treatment that ranged from 7 to 20 weeks. An improvement was observed within 4 weeks of drug initiation. Seventy-nine per cent of the patients showed an objective improvement within 2 months; however, at this dose, 35% of the patients discontinued therapy due to toxicity.

RANDOMIZED TRIALS

Based on these open studies, randomized placebo-controlled trials were initiated to determine the short-term efficacy of MTX in active RA. All of the randomized, placebo-controlled trials were similar with regard to the severity of disease, duration of disease and prior second-line therapy usage. All patients in these studies had failed to respond to or had developed toxicities to second-line therapies, including gold salts and D-penicillamine. Thompson *et al.* [12] reported a placebo-controlled, randomized trial of 48 patients with RA. The dose of parenteral MTX was either 10.0 or 25.0 mg/week. After 6 weeks, a significant improvement was noted in RA activity parameters in the MTX group compared with the placebo group. This improvement included the number of painful joints, swollen joints, global assessment and erythrocyte sedimentation rate.

In 1985, Weinblatt *et al.* [13] reported the results of a placebo-controlled, 24-week, randomized crossover study involving 35 patients. All patients had previously received gold therapy and 80% had previously received D-penicillamine. The initial dose of MTX in this study was 7.5 mg/week, taken in a cycled oral regimen. The dose was increased to six tablets per week or 15.0 mg/week if a clinical response was not noted after 6 weeks. A significant improvement was observed at 12 weeks in the MTX group compared with the placebo group in all clinical variables, with the exception of grip strength. In the MTX group, the mean number of painful joints decreased from 37 at baseline to 11 at 12 weeks, and the number of swollen joints decreased from 34 at baseline to 20 at 12 weeks. The improvement with MTX was noted as early as 3 weeks after drug initiation. Individual patient response, defined as a 50%, or greater, improvement in the joint tenderness index or joint swelling index, occurred in 54 and 34% of the MTX-treated patients. During the second half of the study (weeks 12–24), an increase in disease activity occurred in those patients who initially received MTX and were then randomized to the placebo group.

In an 18 week, randomized, multicentre trial, 189 patients received either placebo or low-dose weekly MTX [14]. In this study, MTX was administered as a weekly, oral cycled regimen at doses of 7.5 or 15.0 mg/week. At 18 weeks, a significant improvement in all disease variables was observed in the MTX group compared with placebo. The mean number of painful joints decreased from 27 to 13 and the number of swollen joints decreased from 22 to 14 in the MTX group, with no change in the placebo-treated patients. Individual patient improvement, defined as a 50% improvement in the joint pain index and joint swelling index, was observed in 32 and 21% of the MTX-treated patients compared with 11 and 4% of the patients who received placebo.

A fourth randomized, placebo-controlled trial also utilized a crossover design [15]. A similar improvement with MTX was observed during the treatment phase with MTX. A flare of disease activity was also noted when patients were randomized from MTX to placebo therapy in the second half of the study.

A meta-analysis was performed of the four randomized trials; a significant improvement was noted in the MTX-treated patients in all clinical parameters, with the exception of the 50′ walk time [16]. A pooled estimate of clinical benefit was defined as the improvement observed in the MTX-treated patients above that observed in the patients who received placebo. By this definition, a 44% reduction in duration of morning stiffness, a 27% reduction in the number of painful joints and a 26% reduction in the number of swollen joints was achieved in the MTX-treated patients.

The four randomized trials and the meta-analysis confirm the short-term efficacy of MTX in patients who have failed other standard second-line therapies, including gold salt therapy. Two of the randomized trials [13, 14] were the pivotal studies for the review by the United States Food and Drug Administration for the approval of MTX as a therapy for active RA.

A flare of arthritis follows MTX discontinuation. This was noted first in short-term crossover studies [13, 15], and was confirmed in two longer treatment studies [17, 18]. In one of the longer term studies, 10 patients received 36 months of MTX and were then re-randomized to receive either placebo or MTX [17]. A flare of arthritis activity occurred in all of the patients randomized to the placebo group; this flare occurred within 4 weeks of discontinuing MTX.

COMPARISON STUDIES

The next step in the development programme of MTX was a comparison of MTX with other standard second-line therapies, including azathioprine, parenteral gold salts, oral gold and, most recently, cyclosporin A.

Three trials have compared MTX with azathioprine. All three of the studies utilized patients who had had prior treatment with either gold salts or D-penicillamine. A study involving 42 patients compared MTX with azathioprine for 24 weeks [19]. The maximum dose of MTX in this study was 15 mg/week and the maximum dose of azathioprine was 150 mg/day. An improvement in all clinical outcome variables was noted in both treatment groups; there was no statistical difference in response between treatment groups. There was, however, a trend towards a more marked and rapid improvement in the MTX-treated population. In a second trial, 53 patients were randomized to receive either MTX, at an initial dose of 10 mg/week, or azathioprine, at an initial dose of 100 mg/day [20]. After 24 weeks, both groups showed a significant improvement from baseline in the pain score and functional capacity score, but there was no difference in response between the two groups. Fifty per cent of

the patients withdrew from the study either due to toxicity or lack of drug efficacy. A 48-week, randomized trial of 64 patients compared MTX, at a maximum dose of 15 mg/week, with azathioprine, at a maximum dose of 150 mg/day [21]. At week 24, a significant improvement in clinical disease variables was observed in both treatment groups. An area under the curve of analysis noted a significantly greater improvement in the MTX-treated group in the number of swollen joints, pain score, erythrocyte sedimentation rate and disease activity score compared with the azathioprine group. Clinical response was faster and more sustained with MTX compared with azathioprine. Patient improvement, using a composite disease activity score, noted that 60% of the patients receiving MTX and 35% of the patients receiving azathioprine improved significantly after 24 weeks of therapy. At week 48, 50% of the patients on azathioprine and 76% of the patients receiving MTX had improvement in this patient response index.

Several studies have compared MTX with parenteral gold salts. In one double-blind trial, 40 patients enrolled in a study lasting 26 weeks, which compared aurothiomalate with parenteral MTX [22]. The dose of MTX was 10 mg/week and the dose of aurothiomalate was 50 mg/week. Both drugs were found to be effective with no difference noted between groups. In a 26-week study of 35 patients, again no difference in efficacy was noted between MTX at a dose of 12.5 mg/week or gold sodium thiomalate [23]. A third study of 57 patients compared gold sodium thiomalate (50 mg/week) with MTX (15 mg/week) for 6 months [24]. An improvement in standard clinical variables and erythrocyte sedimentation rate was observed with both treatment groups and, again, there was no difference in response between groups. Because of the small sample size in all of these studies, conclusions regarding relative efficacy between drugs may not be accurate due to the possibility of a type II statistical error.

In a 9 month trial involving 281 patients and comparing MTX with auranofin, MTX was found to be superior to auranofin in improving all measures of disease activity, including the erythrocyte sedimentation rate [25]. Twenty-five per cent of the patients in the MTX group and 34% of the patients in the auranofin group did not complete the 36 week study. Only four of the patients in the MTX group compared with 13 in the auranofin group withdrew because of a lack of efficacy. Seventy per cent of the patients receiving MTX exhibited a marked improvement, defined as a 50% improvement in the joint/pain and tenderness index, and 64% had a similar level of improvement in the joint swelling index. This degree of improvement was significantly greater with MTX than seen with auranofin.

MTX was recently compared with cyclosporin A in a 34-week, multicentre, double-blind study of 264 patients [26]. All patients failed at least one prior second-line therapy. The dose of MTX ranged from 7.5 to 15.0 mg/week and the dose of cyclosporin A was 2.5–5.0 mg/kg/day. Both cyclosporin A and MTX were found to be statistically superior to placebo. MTX was noted to be superior to cyclosporin A in the improvement in the physician and patient global assessments, Health Assessment Questionnaire score, and the tender joint counts.

Felson *et al.* performed a meta-analysis of placebo-controlled and comparative clinical trials to examine the relative efficacy and toxicity of standard second-line therapies used to treat RA. In the initial meta-analysis [27], MTX was found to be similar in efficacy to injectable gold, D-penicillamine and sulphasalazine. An update in 1992 included studies of azathioprine, and noted that MTX had scored among the most efficacious of the drugs with a favourable toxicity profile [28].

LONG-TERM STUDIES

There have been several long-term prospective studies of MTX in RA. Kremer and Phelps [29] reported a sustained clinical response after 90 months of MTX therapy. Of the original 29 patients enrolled in the study, 18 remained in the trial at 90 months. The dose of MTX ranged from 7.5 to 22.5 mg/week. At 90 months, eight of 14 patients had completely discontinued their prednisone dose; a significant reduction in the mean dose of prednisone was seen for the entire group. All standard clinical parameters improved, with the exception of the number of tender joints.

Similar results were observed in another long-term prospective trial [30]. After completion of a 24-week, placebo-controlled crossover study of MTX [13], 26 patients enrolled in a long-term prospective study. After 84 months of therapy, 12 patients (46%) remained in the study [30]. A significant improvement in all standard arthritis disease parameters, including the number of painful and swollen joints, was still observed. The maximum clinical benefit was achieved by 6 months. Eighty-three per cent of the patients demonstrated a marked improvement, defined as a 50% improvement in the joint pain index, and 92% had a marked improvement in the joint swelling index. A sustained clinical response was observed throughout the study. There was no difference in the degree of improvement noted at 12 months *vs* the improvement noted at 84 months. Fifty per cent of the patients were able to discontinue their background prednisone therapy and 33% of the patients were also able to discontinue their background non-steroidal anti-inflammatory drugs. These two studies are the longest prospective studies of any therapy in the treatment of RA.

In a third prospective study, 128 patients received i.m. MTX at a dose that ranged from 5.0 to 25.0 mg/week [31]. Forty-nine patients received treatment for 3 yr. Clinical parameters improved with therapy, although 43 patients withdrew from the study.

One hundred and ninety-one patients enrolled in a prospective study of MTX treatment at a dose that ranged from 5.0 to 15.0 mg/week [32]. The mean duration of MTX therapy was 3–58 months. A significant improvement in all clinical variables and the

erythrocyte sedimentation rate was observed. A definite reduction in background corticosteroid therapy was also noted. In this study, it was projected that the probability of remaining on MTX was 65% at 2 yr and 46% at 5 yr.

Following completion of a 9-month randomized trial, comparing MTX with auranofin [25], 123 patients enrolled in a 5 yr open study of oral MTX [33]. At year 5, 64% of the patients still remained on drug treatment. A significant improvement was observed in all clinical parameters and the erythrocyte sedimentation rate. There was also a significant improvement noted in the functional status, as assessed by the Modified Health Assessment Questionnaire. A marked improvement, defined as a 50% reduction in the joint pain index and joint swelling index, was observed in 71 and 69% of the patients, respectively. Sixty-two per cent of the patients achieved the Paulus criteria for response [34]. Of the 78 patients with an elevated erythrocyte sedimentation rate at baseline, 51% normalized their sedimentation rate while on treatment. Of the 44 patients who withdrew from the study, only eight withdrew due to a lack of drug efficacy. This high retention rate is highly favourable and is similar to those reported in other prospective studies.

Several retrospective studies have also reported a high retention rate with MTX. Of 124 patients treated with MTX, 60 (48%) continued to receive MTX for 2 yr [35]. Adverse drug reactions were the major reason for drug withdrawal. In a study of 152 patients with RA, 71% of the patients remained on drug at 1 yr; it was projected that, at 6 yr, 49% of the patients would remain on drug treatment [36]. The major reason for withdrawal in this study was also drug toxicity. Studies from community-based rheumatologists from the USA and Australia reported similar high retention rates. Pincus *et al.* [37] reported that the rate of MTX continuation was approximately double that seen with other second-line treatments. Wolfe *et al.* [38] prospectively followed 671 RA patients over a 14-yr observation period. The mean duration of MTX treatment was approximately double that seen with other second-line therapies. In a report from Australia of 596 patients, managed over a decade in community-based practices, it was projected that at 5 yr, 62% of the patients would remain on MTX [39]. This was significantly longer than seen with all other second-line therapies. In another Australian study of 587 patients who received MTX, 76% remained on the drug at 70 months [40]. The majority of terminations were again due to drug toxicity.

DOSING AND DRUG ADMINISTRATION

MTX should not be given more frequently than 1 day/week. More frequent administration is associated with a greater incidence of acute and chronic toxicity, particularly liver disease. MTX can be administered either orally or by parenteral injection. The initial dose of MTX is generally 7.5 mg/week. If a positive result has not been noted within 4–8 weeks and there is no toxicity, the dose may be increased. Most clinical trials utilized doses that ranged from 7.5 to 20.0 mg/week. In the randomized trial comparing auranofin with MTX, 43% of the MTX patients increased their MTX dose from 7.5 to 15.0 mg/week [25]. Furst *et al.* [41] performed a dose–response study in which the 10 mg/m^2 dose was clinically and statistically superior to placebo. There was a suggestion that this dose was better than the 5.0 mg/m^2 dose. As a result of decreased oral bioavailability, MTX doses >20 mg/week should be administered parenterally. A pilot study evaluated i.v. MTX at an initial dose of 40 mg/m^2 in 10 patients who had failed oral MTX [42]. The final dose in this 12 week study was 26 mg/m^2. This higher dose was associated with an improvement in clinical parameters, and side-effects were mild.

Once a satisfactory clinical response occurs, the dose of MTX may be slowly reduced; however, some patients may require higher doses over time to maintain a positive benefit. It has also been observed that some patients can be maintained on therapy every other week without a flare of disease activity.

RADIOGRAPHIC STUDIES

The effect of MTX on radiographic progression has been reported in several studies. In an open study without a control group, a healing of erosions was observed within the first 29 months of MTX therapy [43]. However, in this same population, after a mean of 54 months of treatment, new erosions were noted [44]. In another prospective study, after a mean of 28 months of therapy, a worsening of the radiographs was noted in six of 14 patients [45]. In five patients, an improvement in the number and size of erosions was observed, but a marked narrowing of the joint space was also seen. Two other studies suggested a slowing of radiological progression in a small number of patients [31, 46]. In a multicentre study comparing MTX with azathioprine, the rate of radiographic progression was less in the MTX group than in the azathioprine group [47]. In the 9-month MTX *vs* auranofin study, a decrease in the rate of radiographic progression, as defined by joint erosions and joint space narrowing, was observed with MTX compared with auranofin [48]. In a trial comparing auranofin and MTX alone with the combination of MTX and auranofin, a worsening in the erosion score and joint narrowing score occurred in all three treatment groups [49]. The worsening of erosions and joint narrowing score was statistically significant, however, only in the auranofin group. This study suggested that the rate of progression was also slower with MTX.

CONCLUSIONS

In summary, open prospective studies, short-term randomized placebo-controlled trials, comparison studies of MTX with other second-line therapies and long-term prospective trials all demonstrate the efficacy of low-dose weekly MTX in the treatment of active RA. The high proportion of patients remaining on drug therapy in the prospective studies, and the high retention rate observed from studies by academic and

community-based rheumatologists confirm the long-term efficacy of the compound. MTX has now become a standard therapy in the USA for the treatment of active RA, with increasing enthusiasm for this drug worldwide.

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