

## SHORT REPORT

## Low dose oral methotrexate treatment of multiple sclerosis: a pilot study

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### Abstract

**An 18-month double-blind treatment of multiple sclerosis with low dose oral methotrexate showed it to be well tolerated and suggested effectiveness in exacerbating-relmitting MS but not in the exacerbating progressive and chronic progressive stages.**

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Multiple sclerosis (MS) has been treated with immunological altering methods and drugs for the past two decades. Some appear to be beneficial but problems with administration, cost, side effects, the need for laboratory studies, delayed effectiveness, poor patient acceptance and compliance and the possibility of remote cancer, have limited their use.

Methotrexate in low dose format has been used to treat psoriasis and rheumatoid arthritis for four decades. It may be the most effective and least harmful treatment for progressive rheumatoid arthritis.<sup>1</sup> A trial of low dose methotrexate for MS seemed reasonable. Oral methotrexate was previously evaluated by Neumann and Ziegler<sup>2</sup> who gave 15 patients 2.5 mg of oral methotrexate daily alternating with 6-mercaptopurine in three-month time periods over 10 to 24 months. When compared with a placebo group no obvious difference was noted.

### Method

Approval for the trial was given by the University Human Investigation Committee. Requirements for inclusion were the presence of definite MS, a worsening in function or an exacerbation in the previous year, understanding and willingness to cooperate and no history or evidence of renal or hepatic disease, gross obesity or diabetes. All types of MS were accepted in an attempt to obtain 50 participants in the one year enrolment period. The initial 12 months active treatment period was changed to 18 months during the study on advice of the National Multiple Sclerosis Society. Three participants were unwilling to extend their time in the active phase of the study from 12 to 18 months and six dropped from the treatment phase of the study before 12 months, usually because of inadequate understanding.

One of us (AFH) acted as the 'blind' evaluator and the other (RDC) as the treating physician who might if necessary break the 'blind', a need that occurred twice. The patients were randomised as they entered the study.

The medication was given as one tablet (2.5 mg methotrexate or placebo) every 12 hours for three consecutive doses, once a week (7.5 mg/week); the usual treatment regime for rheumatoid arthritis. Complete blood counts, complete blood chemical analyses and chest radiographs were carried out at the beginning and end of the study. Blood counts and liver function studies were done every two months. Neurological examinations were done at entry, every four months and at the end, and graded on the Kurtzke<sup>3</sup> scale. Additional treatments such as corticosteroids were allowed and were given for exacerbations during the study.

Forty-five patients were enrolled for a period of a year. One took a single pill and dropped out. The remaining 44 were included in the analysis. The time in the study of the six who stopped the medication before the 12 month point was included. At the end of the study the 'blinded' physician categorised the patients into subtypes of MS and tabulated the number and timing of exacerbations and worsenings by one point or more on the Kurtzke scale. An exacerbation

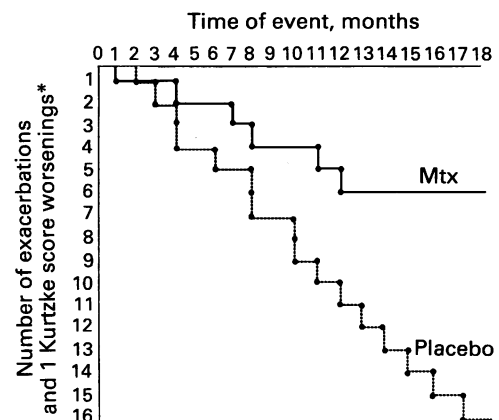


Figure Exacerbations and worsenings of multiple sclerosis of one Kurtzke grade or more in the exacerbating-relmitting methotrexate group (nine patients) and the placebo group (11 patients). \*If a patient had both an exacerbation and a Kurtzke worsening in the same month, it was counted as a single event.

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lasting at least two weeks followed by incomplete or complete recovery and so judged by an experienced neurologist.

Fisher's Exact Test was used to look for an association between the placebo and methotrexate treatments and the proportion of subjects having exacerbations. The two-sample *t* test was used to compare the mean difference in the number of exacerbations between the treatment and placebo groups and to compare the mean difference in the number of exacerbations plus Kurtzke worsenings greater than one between the methotrexate and placebo portions of the exacerbating-remitting group.

### Results

When considered as a single group there was no difference in outcome of the 22 methotrexate and 22 placebo patients. Eight on methotrexate and nine on placebo had exacerbations. Of the 44, 20 had exacerbating-remitting MS and 24 chronic MS including 18 exacerbating progressive, three chronic progressive and three spinal patients. In the exacerbating-remitting group of 20 (11 placebo, nine methotrexate) there were 14 females and six males, median age 39.5 years. In the 12 months before the study there were 12 exacerbations in the 11 placebo patients and nine in the nine methotrexate patients. During treatment a total of three exacerbations occurred in two of the nine exacerbating-remitting methotrexate patients over a period of 150 treatment months, for a mean of one exacerbation per 50 months. Seven of the 11 placebo patients had 12 exacerbations during 169 total group treatment months, a mean of one per 14 months. The difference in proportions of patients having exacerbations is not significant ( $p = 0.09$ ) while the difference in the mean number of exacerbations just reaches significance with  $p = 0.05$ . Three of the nine methotrexate patients and five of 11 placebo patients worsened by one or more points on the Kurtzke scale.

The figure shows the time of exacerbations and worsenings of one Kurtzke grade or more in the exacerbating-remitting methotrexate and placebo groups. The placebo group had 16 events which continued to occur to the end of the study (three placebo patients experienced an exacerbation and a Kurtzke grade worsening simultaneously which were considered as one event in each case) and the methotrexate group had six events, with no worsenings after 12 months. The difference in the mean number of exacerbations plus Kurtzke score worsenings of one or more is just significant with  $p = 0.05$ .

There were 24 patients (11 placebo, 13 methotrexate) in the chronic MS group, 19 female and five male, median age 46.8 years. The three early dropouts at four, five and eight months were all on placebo. Total treatment times were 156 months for placebo and 230 for methotrexate.

Two of 11 patients on placebo had a total of three exacerbations in 156 months of treatment, one per 52 months, and six of 13

methotrexate patients had a total of nine exacerbations in 230 months of treatment, or one every 25.5 months. Two of 13 methotrexate patients worsened by one or more points on the Kurtzke scale and none of the 11 placebo patients worsened by one point or more.

While none of the outcome variables nears statistical significance in the chronic MS group ( $p = 0.15$  for the difference in proportions with exacerbations and  $p = 0.11$  for the difference in the number of exacerbations), it may be important to notice that the direction of the differences is opposite to the exacerbating-remitting group.

The methotrexate was tolerated reasonably well. Two patients complained of headaches, both were on placebo. Nausea was helped by taking the medication with meals. One methotrexate patient had moderate hair thinning. Liver enzymes became mildly to moderately abnormal on more than one occasion in eight methotrexate and one placebo patients but were persistently abnormal in only one methotrexate patient. In that patient the medication was stopped, the enzymes returned to normal and the medication was restarted with the enzymes remaining normal.

### Discussion

The effect of methotrexate on the liver has been a concern over the years. It is proving to be less toxic than originally thought, and the rheumatologists, the chief users of oral low dose therapy, are gradually using fewer tests of hepatic function. In a recent five year study of low dose methotrexate in the treatment of rheumatoid arthritis,<sup>4</sup> 44 of 124 patients stopped the treatment because of side effects including nausea, stomatitis, hair loss, rash, pulmonary reactions, elevated liver enzymes, haematological abnormalities and hepatic fibrosis. Although 93% of the total experienced at least one drug reaction the majority did not require permanent drug discontinuation. There is no evidence that low dose methotrexate causes cancer.

In the present study those with exacerbating-remitting MS apparently benefited and those with chronic MS worsened. Why did not the methotrexate benefit both types? The question of dosage is debatable.

This is a small trial and must be considered a preliminary study of low dose oral methotrexate in the treatment of multiple sclerosis. Methotrexate therapy is now under evaluation by others with larger and longer studies which should help determine the truth of the matter.

Lederle Pharmaceuticals kindly provided the methotrexate and placebo for this study and helped defray the cost of the laboratory work.

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