

## A COMPARISON OF METHOTREXATE WITH PLACEBO FOR THE MAINTENANCE OF REMISSION IN CROHN'S DISEASE

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**ABSTRACT**

**Background** Patients with Crohn's disease often have relapses. Better treatments are needed for the maintenance of remission. Although methotrexate is an effective short-term treatment for Crohn's disease, its role in maintaining remissions is not known.

**Methods** We conducted a double-blind, placebo-controlled, multicenter study of patients with chronically active Crohn's disease who had entered remission after 16 to 24 weeks of treatment with 25 mg of methotrexate given intramuscularly once weekly. Patients were randomly assigned to receive either methotrexate at a dose of 15 mg intramuscularly once weekly or placebo for 40 weeks. No other treatments for Crohn's disease were permitted. We compared the efficacy of treatment by analyzing the proportion of patients who remained in remission at week 40. Remission was defined as a score of 150 or less on the Crohn's Disease Activity Index.

**Results** Forty patients received methotrexate, and 36 received placebo. At week 40, 26 patients (65 percent) were in remission in the methotrexate group, as compared with 14 (39 percent) in the placebo group ( $P=0.04$ ; absolute reduction in the risk of relapse, 26.1 percent; 95 percent confidence interval, 4.4 percent to 47.8 percent). Fewer patients in the methotrexate group than in the placebo group required prednisone for relapse (11 of 40 [28 percent] vs. 21 of 36 [58 percent],  $P=0.01$ ). None of the patients who received methotrexate had a severe adverse event; one patient in this group withdrew because of nausea.

**Conclusions** In patients with Crohn's disease who enter remission after treatment with methotrexate, a low dose of methotrexate maintains remission. (N Engl J Med 2000;342:1627-32.)

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**C**ROHN'S disease is a chronic inflammatory disorder of the gastrointestinal tract. Since the cause of the disease is unknown,<sup>1-4</sup> non-specific antiinflammatory agents such as corticosteroids are frequently prescribed.<sup>5-7</sup> However, the long-term use of corticosteroids is poorly tolerated.<sup>8-10</sup> Therefore, a safe and effective long-term treatment that eliminates the need for corticosteroids is desirable. Although purine antimetabolites (mercaptopurine and azathioprine)<sup>11-13</sup> are moderately effective, the disease often relapses despite treatment with these agents.

When used as therapy for rheumatoid arthritis, methotrexate frequently reduces or eliminates the need for corticosteroids.<sup>14-16</sup> Therefore, it is reasonable to hypothesize that it may yield similar benefits for patients with Crohn's disease. Although methotrexate does induce remission in patients with Crohn's disease,<sup>17</sup> long-term trials have not been performed in patients with quiescent disease. Therefore, we evaluated the use of methotrexate as a maintenance therapy in patients whose Crohn's disease was in remission.

**METHODS****Patients**

This randomized, placebo-controlled trial was conducted at seven university medical centers in North America. Investigators and patients were unaware of the treatment assignments. The protocol was approved by the institutional review board at each center. All patients gave written informed consent.

The characteristics of eligible patients have been described previously.<sup>17</sup> Briefly, patients had to have chronically active Crohn's disease and to have no risk factors for methotrexate-induced toxicity,<sup>18,19</sup> including hepatic disease, consumption of more than seven alcoholic drinks per week, weight more than 40 percent above normal, diabetes mellitus, renal dysfunction (defined as a serum creatinine concentration of more than 1.7 mg per deciliter [150  $\mu$ mol per liter]), clinically important lung disease, systemic infection, pregnancy or a desire to become pregnant, history of cancer, or hypersensitivity to methotrexate. Patients with an estimated survival of less than one year and those who were unwilling to comply with the protocol were not eligible. The patients also had to have entered remission after treatment with 25 mg of methotrexate once weekly by intramuscular injection for a minimum of 16 weeks. Remission was defined as both the absence of the need for prednisone therapy and the presence of a score of 150 or less on the Crohn's Disease Activity Index. This index incorporates eight items: the number of liquid or very soft stools in the seven days preceding the assessment, the severity of abdominal pain, general well-being, the presence or absence of an abdominal mass or extraintestinal manifestations of disease, the use of opiates to treat

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diarrhea, hematocrit, and weight. Scores on this index can range from 0 to approximately 600. Higher scores indicate greater disease activity. A score of 150 or less is considered to indicate inactive disease, and a score of more than 450 to indicate critical illness. A decrease of 70 to 100 points is clinically meaningful.<sup>5,7</sup>

Patients entered the study in one of two ways. From March 1993 to February 1994 those who participated in a randomized trial of methotrexate for active Crohn's disease<sup>17</sup> were eligible if they had stopped taking prednisone and were in remission at the end of the study. After February 1994 (i.e., from August 1994 to September 1997), patients who had met the entry criteria for the randomized trial and who had entered remission after 16 to 24 weeks of open-label methotrexate (25 mg once weekly) were also eligible.

### Base-Line Studies

One week before the randomization visit, patients began recording on diary cards the data necessary to calculate the Crohn's Disease Activity Index.<sup>20</sup> During the randomization visit, demographic information was obtained, a physical examination and blood tests were performed, and the score on the Crohn's Disease Activity Index was calculated.

### Randomization

The patients were randomly assigned, with use of a computer-generated schedule, to receive weekly intramuscular injections of either 15 mg of methotrexate (Rheumatrex, Wyeth-Ayerst, Montreal) or an identical-appearing placebo for 40 weeks. The randomization schedule was stratified according to center and used random numbers in permuted blocks of four. Between study visits, injections were administered by a family physician.

### Other Treatments for Crohn's Disease

Patients were not permitted to use immunosuppressive agents, corticosteroids, infliximab, aminosaliclates, antibiotics, tube feeding, or parental nutrition. The use of hydrocortisone ointment was allowed for perianal disease.

### Follow-up

Patients were assessed every four weeks. At each visit, the score on the Crohn's Disease Activity Index was calculated and blood was obtained for chemical analyses. The study medication was discontinued if treatment for active Crohn's disease was prescribed. Patients who discontinued the study medication because of adverse drug reactions or treatment failure were followed in the same manner as those who continued to receive the injections. Drug treatments and doses were recorded at each visit. Folic acid was not routinely administered, but treatment was commenced (1 mg daily) if adverse events occurred that were thought to be due to methotrexate. A physician who was aware of the group assignments but who had no contact with the patients and who did not assess outcomes monitored serum aminotransferase levels<sup>18</sup> and complete blood counts. The results of these tests were not available to the attending physicians or nurses. If leukopenia developed (defined as a white-cell count of  $3.8 \times 10^3$  per cubic millimeter or less), the study drug was withheld for one week and the dose was decreased to 12.5 mg the following week. Treatment was discontinued if leukopenia persisted. A similar approach was adopted if the serum aminotransferase concentrations increased to twice the upper limit of the normal range. To maintain blinding, matched dose adjustments were made in the placebo group.

### Outcome Measures

The primary measure of response was the occurrence of a relapse of Crohn's disease, defined as an increase in the Crohn's Disease Activity Index score of at least 100 points above the base-line value or the initiation of prednisone, an antimetabolite, or the two in combination for the treatment of symptoms of Crohn's disease. Patients could meet one or both criteria. Clinical data were independently reviewed by two investigators who were unaware of the

patients' treatment assignments. Disagreements between reviewers regarding the validity of a relapse were resolved by consensus. A secondary outcome was the need for prednisone. Among the patients who relapsed, the proportion who reentered remission after treatment with methotrexate at a higher dose (25 mg once weekly) was assessed. Adverse drug reactions were evaluated by physicians who were unaware of the patients' treatment assignments and were classified with respect to the likelihood of a causal relation to the study drug and severity according to the standard criteria of the World Health Organization. In this system, a grade of 0 indicates the absence of toxic effects, a grade of 1 the presence of mild effects, a grade of 2 the presence of moderate effects, a grade of 3 the presence of severe effects, and a grade of 4 the presence of life-threatening effects.

### Statistical Analysis

Base-line characteristics were analyzed with the use of descriptive statistics. In the primary analysis, we used logistic-regression analysis to compare the proportions of patients in each group who remained free of a relapse during the 40 weeks of follow-up. The design factors — the route of entry into the trial (from the randomized, controlled trial or from the open-label study) and study center — were included in the model. We also examined other potential prognostic variables (age, sex, site of disease, and smoking status). We used Kaplan–Meier product-limit methods to estimate the median duration of remission. Cox regression analysis was performed to control for the previously identified design factors and prognostic variables. We used Fisher's exact test to compare the proportions of patients who received prednisone in each group. These analyses were performed in accordance with the intention-to-treat principle. We used Fisher's exact test to compare the number of patients with adverse events in each group. Statistical analyses were performed with SAS software.<sup>21</sup> A two-sided P value of 0.05 or less was considered to indicate statistical significance.

We estimated that 80 percent of the patients in the placebo group would have a relapse. Randomization of 110 patients would give the study a power of 80 percent to detect a clinically important absolute difference of 25 percent in the primary outcome between the study groups. However, the rate of recruitment was slower than expected, since many patients who had been successfully treated with open-label methotrexate were unwilling to participate in a placebo-controlled trial. For administrative reasons (primarily the impending unavailability of the study drugs because we were unable to locate a manufacturer that could continue to supply methotrexate and placebo according to the necessary specifications), enrollment was stopped after 76 patients had undergone randomization. This number of patients gave the study a power of 68 percent to detect an absolute difference of 25 percent between the treatment groups.

## RESULTS

### Randomization

Between March 1993 and September 1997, 125 patients were assessed for eligibility. Thirty-eight patients did not provide informed consent. The presence of a previously unidentified risk factor for methotrexate-induced toxicity (in the case of five patients), the use of contraindicated medication (in the case of four) and a weight that was more than 40 percent above normal (in the case of two) were other reasons for exclusion. Of the 76 eligible patients, 23 were enrolled from the randomized trial and 53 were enrolled from the open-label study with methotrexate. Overall, 40 patients were randomly assigned to receive methotrexate and 36 to receive placebo. The characteristics of the two groups were similar (Table 1).

**Primary Outcome**

One patient in the methotrexate group was lost to follow-up. Fewer patients in the methotrexate group than in the placebo group discontinued treatment before the 40-week study ended (17 of 40 [42 percent] vs. 23 of 36 [64 percent],  $P=0.06$ ). The proportion that discontinued treatment because of an adverse drug reaction was similar in the two groups (one patient in the methotrexate group and none in the placebo group).

After 40 weeks, the proportion of patients who remained in remission was higher in the methotrexate group than in the placebo group (26 of 40 [65 percent] vs. 14 of 36 [39 percent]; unadjusted  $P=0.04$ ;  $P=0.01$  after adjustment for the route of entry into the trial and study center; absolute reduction in the risk of relapse, 26.1 percent; 95 percent confidence interval, 4.4 percent to 47.8 percent). Seventy-eight percent of the relapses met both criteria for relapse; 22 percent met only the criterion of the need for treatment of active disease. None of the potential prognostic variables evaluated were significantly associated with relapse. The median duration of remission was estimated to be 22 weeks in the placebo group (Fig. 1). Fewer than 50 percent of the patients in the methotrexate group had relapsed by the end of the study. Therefore, the median duration of remission in this group could not be determined, but it was longer than 40 weeks. In the Cox

regression model, treatment with methotrexate was significantly associated with the duration of remission with or without adjustment for the effects of study center and route of entry into the study (adjusted and unadjusted  $P=0.04$ ).

**Use of Prednisone for Relapses**

Patients in the methotrexate group had fewer relapses than those in the placebo group and thus were less likely to receive prednisone. Eleven patients (28 percent) in the methotrexate group received prednisone, as compared with 21 patients (58 percent) in the placebo group ( $P=0.01$ ). Among the patients who received prednisone, the total dose of prednisone and the average duration of use were similar in the two groups: 2242 g and 126 days in the methotrexate group and 2071 g and 122 days in the placebo group.

**Treatment with Methotrexate after Relapse**

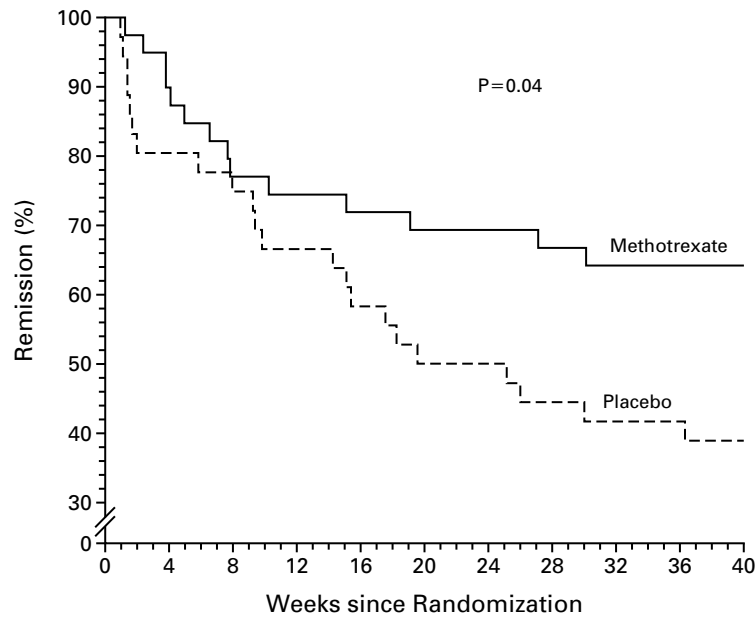
Of the 36 patients who relapsed (14 in the methotrexate group and 22 in the placebo group), 22 patients (61 percent) were subsequently given 25 mg of methotrexate once weekly, usually in addition to prednisone. Twelve of these 22 patients (55 percent) successfully discontinued prednisone and were in remission at week 40. Conversely, of the 14 patients who did not receive methotrexate after relapse, only 2 patients (14 percent) were in remission at week 40.

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS OVERALL AND ACCORDING TO WHETHER THEY ENROLLED IN THE STUDY AFTER COMPLETING A RANDOMIZED TRIAL OF METHOTREXATE OR OPEN-LABEL TREATMENT.\***

CHARACTERISTIC	ALL PATIENTS		PATIENTS FROM THE RANDOMIZED TRIAL		PATIENTS FROM THE OPEN-LABEL STUDY	
	METHOTREXATE (N=40)	PLACEBO (N=36)	METHOTREXATE (N=12)	PLACEBO (N=11)	METHOTREXATE (N=28)	PLACEBO (N=25)
Age — yr	32±2	34±2	35±3	35±2	30±2	33±3
Male sex — no. (%)	16 (40)	22 (61)	6 (50)	8 (73)	10 (36)	14 (56)
Months since diagnosis	88±10	84±10	81±19	79±15	91±13	87±13
Disease site — no. (%)						
Colon	11 (28)	9 (25)	3 (25)	3 (27)	8 (29)	6 (24)
Small bowel	18 (45)	11 (31)	6 (50)	2 (18)	12 (43)	9 (36)
Both	11 (28)	16 (44)	3 (25)	6 (55)	8 (29)	10 (40)
Abdominal mass — no. (%)	1 (2)	2 (6)	0	0	1 (4)	2 (8)
Previous surgery for Crohn's disease — no. (%)	17 (43)	13 (36)	7 (58)	4 (36)	10 (36)	9 (36)
Previous treatment with purine antimetabolites — no. (%)	1 (2)	1 (3)	0	0	1 (4)	1 (4)
Cigarette smoker — no. (%)	20 (50)	15 (42)	4 (33)	9 (82)	16 (57)	6 (24)
Crohn's Disease Activity Index score†	94±7	84±7	91±13	83±14	95±8	84±8
White-cell count — ×10 <sup>-3</sup> /mm <sup>3</sup>	8.0±0.3	7.4±0.4	8.8±0.9	7.4±0.5	7.8±0.4	7.4±0.5
Hemoglobin — g/liter	132±2	133±2	129±5	137±4	134±3	131±3
Platelet count — ×10 <sup>-3</sup> /mm <sup>3</sup>	330±17	323±14	354±32	320±29	323±20	324±16

\*Plus-minus values are means ±SE. There were no significant differences between the groups.

†Higher scores indicate greater disease activity. Scores of 150 or less indicate that the disease is in remission.



NO. AT RISK		0	4	8	12	16	20	24	28	32	36	40
Methotrexate	40	36	30	29	28	27	27	26	25	24	19	
Placebo	36	29	28	24	21	18	18	16	15	15	12	

**Figure 1.** Kaplan–Meier Estimates of the Time to Relapse in the Methotrexate Group and the Placebo Group.

The P value was derived from a Cox regression model that was adjusted for the effects of the route of entry into the study and the study center. The unadjusted P value was 0.04.

### Adverse Events

None of the patients in the methotrexate group had a severe adverse event, as compared with two in the placebo group (one had cervical dysplasia, and the other had a viral respiratory tract infection). One patient who received methotrexate withdrew from the trial prematurely because of nausea. Although nausea and vomiting occurred more frequently among patients in the methotrexate group (Table 2), none of the symptoms were severe, and only one patient discontinued treatment because of these symptoms. No patient had leukopenia that was severe enough to require withholding treatment or withdrawal from the study. The overall incidence of adverse events was similar in the two groups.

### DISCUSSION

We found methotrexate to be an effective and safe maintenance therapy for patients with Crohn's disease. Before enrolling in this study, the patients had entered clinical remission and had stopped taking prednisone after 16 to 24 weeks of therapy with methotrexate. Over the next 10 months significantly more patients in the methotrexate group than in the placebo group remained in remission. Moreover, 72 percent of the patients in the methotrexate group did

not require prednisone treatment for recurrent symptoms, as compared with 42 percent of those in the placebo group. In addition, retreatment with a higher dose of methotrexate (25 mg), usually in combination with prednisone, induced remission in over half the patients who had relapsed. Although these data are observational and thus should be interpreted with caution, our findings suggest that many patients who relapse while receiving low-dose maintenance therapy with methotrexate might ultimately be able to discontinue prednisone therapy if the dose of methotrexate is increased. Because of the long-term consequences of prolonged corticosteroid<sup>8-10</sup> therapy, maintenance therapy with methotrexate may be preferable.

Notwithstanding previous data that support the efficacy of methotrexate for patients with corticosteroid-dependent Crohn's disease,<sup>17,22</sup> the purine antimetabolites remain the most frequently prescribed drugs for this group of patients. This practice is based on evidence from the three randomized trials of long-term antimetabolite therapy that used adequate doses.<sup>11-13</sup> In these studies, which evaluated 41 to 72 patients for at least one year, 42 to 47 percent of patients who received antimetabolite therapy were in remission and were not taking prednisone at the com-

TABLE 2. INCIDENCE OF ADVERSE EVENTS.\*

ADVERSE EVENT	METHOTREXATE	PLACEBO
	(N=40)	(N=36)
	no. of patients (%)	
Nausea and vomiting	16 (40)	9 (25)
Symptoms of a cold	10 (25)	10 (28)
Abdominal pain	7 (18)	9 (25)
Headache	7 (18)	6 (17)
Joint pain or arthralgia	5 (12)	10 (28)
Fatigue	5 (12)	5 (14)
Influenza-like illness	2 (5)	2 (6)
Diarrhea	1 (2)	7 (19)
Abdominal bloating or distention	1 (2)	1 (3)
Rash	2 (5)	4 (11)
Insomnia	1 (2)	0
Other	17 (43)	15 (42)

\*Patients may have had more than one adverse event.

pletion of follow-up, as compared with 6 to 14 percent of patients in the placebo group. In the trial whose design most resembled the design of our study, O'Donoghue et al.<sup>12</sup> assigned 52 patients in remission to receive either azathioprine (2.0 mg per kilogram of body weight per day) or placebo. After one year, the remission rates were only 42 percent in the azathioprine group and 6 percent in the placebo group ( $P=0.001$ ). These data underscore two issues that are relevant to the interpretation of our results. First, since the rate of relapse is high despite therapy with purine antimetabolites, many patients are candidates for treatment with another agent, such as methotrexate. Second, the relapse rates in the placebo groups of the other trials were substantially higher than the rate in our study. One possible explanation for this difference is that the regimen of methotrexate administered before entry into our trial may have induced healing of the intestinal mucosa,<sup>22</sup> resulting in a sustained clinical benefit. To investigate this possibility, studies that include endoscopic assessment should be performed. Alternatively, our patients may have been less ill than those evaluated in the other trials. We believe this latter explanation to be unlikely, since all of our patients had been dependent on corticosteroids for long periods before treatment with methotrexate was begun.<sup>23-25</sup>

In the absence of good comparative data, clinicians must decide whether methotrexate or a purine antimetabolite is preferable for their patients.<sup>26</sup> Although there is an extensive and satisfactory long-term experience with the purine antimetabolites in Crohn's disease,<sup>27,28</sup> these drugs have a gradual onset of action. Methotrexate has been preferred to azathioprine for the treatment of rheumatoid arthritis because it has

a more rapid clinical effect and superior long-term tolerability.<sup>29-32</sup> Methotrexate was well tolerated in our study. Although nausea and vomiting were more prevalent among the patients in the methotrexate group, these symptoms were typically mild. However, our patients were already in remission after treatment with methotrexate and were therefore preselected with respect to their tolerance of the drug.

The risk of liver disease from methotrexate therapy remains an issue. The incidence of serious hepatic toxicity is sufficiently low among patients with rheumatoid arthritis who receive methotrexate that surveillance liver biopsy is no longer recommended.<sup>33-35</sup> In the absence of biopsy data from patients with Crohn's disease, these patients should be monitored for hepatic toxicity during treatment with methotrexate.<sup>36</sup> Physicians must also be aware of the potentially serious complications of hypersensitivity pneumonitis<sup>37</sup> and bone marrow depression.<sup>38</sup> Methotrexate must not be prescribed to women of child-bearing potential, because of the risk of teratogenicity.<sup>39,40</sup>

In conclusion, in this placebo-controlled trial, we have shown that methotrexate is a safe treatment for the maintenance of remission induced by methotrexate in patients with Crohn's disease.

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## APPENDIX

In addition to the authors, the following persons and institutions participated in the North American Crohn's Study Group: External Advisory Committee — R. Kozarek, A. Laupacis, J. Singleton, and D. Sackett (chair); unblinded clinicians — V. Bain, G. Galler, C. Ghent (chair), E.J. Heathcote, J. Lemaire, G. Sweeney, and C. Watts; coordinating center — B. Bergman and E. Liddiard; centers (listed with the number of patients enrolled in parentheses): University of Western Ontario, London (45) — P. Adams, W. Barnett, M. Belsheim, D. Bondy, R. Eberhard, P. Gilmore, J. Howard, D. Lloyd, L. Moyer, T. Ponich, H. Preiksaitis, I. Prokopiw, R. Reynolds, and W. Watson; McGill University, Montreal (13) — J.F. Bernard, A. Bitton, A. Cohen, D.S. Daly, L. Dionne, M. Lichter, and S. Mishkin; University of Alberta, Edmonton (11) — V. Bain, D. Fisher, P. Kirdeikis, E. Lalor, M. Ma, D. Sadowski, R. Sherbaniuk, A. Thomson, and B. Yacyshyn; University of Chicago, Chicago (4); University of Calgary, Calgary, Alta. (1) — N. Hershfield, D. Koegler, and N. Racicot; McMaster University, Hamilton, Ont. (1) — M. Donnelly; University of Winnipeg, Winnipeg, Man. (1) — C. Bernstein and P. Rawsthorne.

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