

## METHOTREXATE FOR THE TREATMENT OF CROHN'S DISEASE

BRIAN G. FEAGAN, M.D., JAMES ROCHON, PH.D., RICHARD N. FEDORAK, M.D., E. JAN IRVINE, M.D., GARY WILD, M.D., LLOYD SUTHERLAND, M.D., A. HILLARY STEINHART, M.D., GORDON R. GREENBERG, M.D., RICHARD GILLIES, M.D., MARYBETH HOPKINS, R.N., STEPHEN B. HANAUER, M.D., AND JOHN W.D. McDONALD, M.D., FOR THE NORTH AMERICAN CROHN'S STUDY GROUP INVESTIGATORS\*

**Abstract Background.** Although corticosteroids are highly effective in improving symptoms of Crohn's disease, they may have substantial toxicity. In some patients, attempts to discontinue corticosteroids are unsuccessful.

**Methods.** We conducted a double-blind, placebo-controlled multicenter study of weekly injections of methotrexate in patients who had chronically active Crohn's disease despite a minimum of three months of prednisone therapy. Patients were randomly assigned to treatment with intramuscular methotrexate (25 mg once weekly) or placebo for 16 weeks. The patients also received prednisone (20 mg once a day), which was tapered over a period of 10 weeks unless their condition worsened. The primary outcome measure was clinical remission at the end of the 16-week trial. Remission was defined by the discontinuation of prednisone and a score of  $\leq 150$  points on the Crohn's Disease Activity Index.

**Results.** A total of 141 patients were randomly assigned in a 2:1 ratio to methotrexate (94 patients) or placebo (47 patients). After 16 weeks, 37 patients (39.4 per-

cent) were in clinical remission in the methotrexate group, as compared with 9 patients (19.1 percent) in the placebo group ( $P=0.025$ ; relative risk, 1.95; 95 percent confidence interval, 1.09 to 3.48). The patients in the methotrexate group received less prednisone overall than those in the placebo group ( $P=0.026$ ). The mean ( $\pm$ SE) score on the Crohn's Disease Activity Index after 16 weeks of treatment was significantly lower in the methotrexate group ( $162\pm 12$ ) than in the placebo group ( $204\pm 17$ ,  $P=0.002$ ). The changes in quality-of-life scores and serum orosomucoid concentrations were similar. In the methotrexate group, 16 patients (17 percent) withdrew from treatment because of adverse events (including asymptomatic elevation of serum aminotransferase in 7 and nausea in 6), as compared with 1 patient (2 percent) in the placebo group.

**Conclusions.** In a group of patients with chronically active Crohn's disease, methotrexate was more effective than placebo in improving symptoms and reducing requirements for prednisone. (*N Engl J Med* 1995;332:292-7.)

CROHN'S disease is an inflammatory disorder that commonly involves the small bowel and colon. Although corticosteroids are highly effective in improving symptoms,<sup>1,2</sup> attempts to discontinue therapy are unsuccessful in approximately 20 percent of patients.<sup>3</sup> Patients treated with corticosteroids continue to have both complications of the disease and chronic toxicity from the therapy.<sup>4-7</sup> Either mercaptopurine or azathioprine is sometimes prescribed to reduce the requirements for corticosteroids, but the toxicity of these medications is of concern.<sup>8-10</sup> Low-dose cyclosporine is not effective in this situation.<sup>11-13</sup> Alternative treatments are desirable.

Methotrexate, an antiinflammatory drug, has been used to treat rheumatoid arthritis<sup>14,15</sup> and psoriasis.<sup>16,17</sup> After a report of improvement in patients with Crohn's disease who were treated with methotrexate,<sup>18</sup> we further assessed the efficacy of methotrexate therapy in chronically active Crohn's disease.

From the Department of Medicine, Division of Gastroenterology, University of Calgary, Calgary, Alta. (L.S.); the Department of Medicine, Section of Gastroenterology, University of Chicago, Chicago (S.B.H.); the Department of Medicine, Division of Gastroenterology, University of Alberta, Edmonton (R.N.F.); the Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Ont. (E.J.I.); the Departments of Medicine (B.G.F., J.W.D.M., M.H.) and Epidemiology and Biostatistics (B.G.F., J.R.), University of Western Ontario, London, Ont.; the Department of Medicine, Division of Gastroenterology, McGill University, Montreal (G.W.); the Department of Medicine, Division of Gastroenterology, University of Toronto, Toronto (A.H.S., G.R.G.); and the Department of Medicine, University of Ottawa, Ottawa, Ont. (R.G.). Address reprint requests to Dr. Feagan at 6 OF 12 University Hospital, 339 Windemere Rd., London, ON N6A 5A5, Canada.

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\*The persons and institutions participating in the North American Crohn's Study Group are listed in the Appendix.

## METHODS

A randomized, double-blind, placebo-controlled study was conducted at seven university medical centers between November 1992 and February 1994. The protocol was approved by the investigational review board at each center. All the patients gave written informed consent.

### Patients

The medical records of potentially eligible patients were reviewed by a clinician, a radiologist, and a pathologist to confirm the diagnosis of Crohn's disease. Eligible patients had chronically active disease with at least three months of symptoms despite daily doses of at least 12.5 mg of prednisone with at least one attempt to discontinue treatment. Patients who had received long-term prednisone therapy at low doses ( $\leq 10$  mg per day) were ineligible, as were critically ill patients.

Patients with the following risk factors for methotrexate toxicity<sup>19</sup> were ineligible: preexisting hepatic disease (biopsy-proved cirrhosis, chronic active hepatitis, or serum aspartate aminotransferase, bilirubin, or alkaline phosphatase concentrations at least twice the upper limit of normal), renal dysfunction (serum creatinine concentration greater than 1.7 mg per deciliter [ $150 \mu\text{mol}$  per liter]), clinically important lung disease as determined subjectively, systemic infection, pregnancy or a desire to become pregnant, history of cancer, high alcohol consumption (more than seven drinks per week), hypersensitivity to methotrexate, erythrocyte macrocytosis, body weight 40 percent higher than normal, diabetes mellitus, a requirement for nonsteroidal antiinflammatory drugs, or the use of immunosuppressive drugs in the past three months. Patients with an estimated survival of less than one year and those who were unwilling to comply with the protocol were also ineligible for the study.

### Base-Line Studies

Three weeks before randomization, potentially eligible patients were instructed in the use of a diary card to score the Crohn's Disease Activity Index.<sup>20,21</sup> This index incorporates eight items: the number of liquid or very soft stools, abdominal pain, general well-being, extraintestinal manifestations of Crohn's disease, the use of opiates to treat diarrhea, abdominal mass, hematocrit, and body weight; these yield a composite score ranging from 0 to approximately 600. Higher scores indicate more disease activity; patients with scores of

150 or less are considered to have inactive disease, whereas those with scores above 450 are critically ill. A clinic visit was scheduled one week later (two weeks before randomization), at which time a physical examination and blood tests were performed and base-line demographic information, scores on the Crohn's Disease Activity Index, and data on prednisone use were obtained. Quality of life was measured with the Inflammatory Bowel Disease Questionnaire, a previously validated instrument with four parts (on bowel function, emotional status, systemic symptoms, and social function); the total score on this index ranges from 32 to 224, with higher scores indicating better quality of life. The scores of patients in remission usually range from 170 to 190.<sup>22,23</sup> Patients were then treated with 20 mg of prednisone once daily. A uniform dose was chosen to control for the effects of a primary determinant of disease activity and to permit a common starting point from which to measure differences in prednisone use between groups.

### Randomization

The patients were randomly assigned, in a 2:1 ratio, to receive either 25 mg of methotrexate (Rheumatrex, Lederle Laboratories, Pearl River, N.Y.) or a placebo weekly for 16 weeks if they had not required increases in their prednisone dose to 20 mg daily in the preceding two weeks. Medication was given by intramuscular injection to ensure drug absorption and minimize nausea. The placebo was identical in appearance to the active drug. Between each patient's visits to the study clinic, the injection was administered by a family physician. The investigators were unaware of the treatment assignments. Patients who were receiving 20 mg or more of prednisone daily two weeks before randomization were randomized in a separate stratum (the high-prednisone stratum) from those who had their dose increased to 20 mg (the low-prednisone stratum). Stratification was used because we predicted that patients who had required higher prednisone doses in the past to control symptoms would have a worse prognosis.

### Prednisone Therapy

For two weeks after randomization, no attempt was made to decrease the prednisone dose. After the first follow-up visit (at week 2), the daily dose of prednisone was decreased by 2.5 mg each week. Prednisone was discontinued by week 12 of the study if the patient's condition remained stable or improved. Patients whose condition worsened had their prednisone dosage increased to a maximal daily dose of 40 mg. After a dose increase, prednisone tapering was resumed at a rate of 5 mg a week until a daily dose of 20 mg was reached. The tapering regimen described above was then begun again.

### Other Treatments for Crohn's Disease

The patients were not permitted to use aminosaliclates, budesonide, immunosuppressive agents, antibiotics for perianal disease, tube feeding, parenteral nutrition, or topical aminosaliclates or corticosteroids. The use of hydrocortisone ointment was allowed for perianal disease.

### Follow-up

Patients were seen 2 and 4 weeks after randomization and every 4 weeks thereafter for 16 weeks. At each visit, the patient's scores on the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire were calculated, and the serum orosomucoid concentration (a laboratory measure of inflammatory activity) and the total prednisone dose were measured. Patients who discontinued their medication because of adverse reactions or treatment failure were followed in the same way as those who continued to receive injections.

A physician who had no contact with patients and did not assess outcomes, but who was aware of the group assignments, monitored serum aminotransferase concentrations each month and complete blood counts every two weeks. These results were not made available to the attending physicians and nurses. If leukopenia developed (white-cell count,  $\leq 3.8 \times 10^9$  per liter), the study drug was withheld for one week and the daily dose was decreased to 17.5 mg the following week. The study drug was discontinued if persistent leukopenia developed. An identical algorithm was followed if the serum amino-

transferase concentrations increased to twice the upper limit of normal. Matching dose adjustments were made in the placebo group.

### Outcome Measures

The primary outcome measure was the presence of clinical remission, as defined by the discontinuation of prednisone therapy and a score on the Crohn's Disease Activity Index of  $\leq 150$  points at the end of the trial (16 weeks). Secondary outcomes were the daily dose of prednisone, the mean scores on the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire, and the mean serum orosomucoid concentration.<sup>24,25</sup>

### Statistical Analysis

Statistical comparisons were made with SAS software.<sup>26</sup> A two-sided P value of 0.05 was the criterion for statistical significance. All analyses were performed according to the intention-to-treat principle. The medical center and stratum of the prednisone dose were used as the stratification variables. Base-line characteristics measured on a nominal or ordinal scale were compared by Fisher's exact test or the chi-square test, and continuous variables were compared by analysis of variance.

In the primary analysis, the proportions of patients in the two study groups who successfully discontinued prednisone and remained in remission at 16 weeks were compared with use of the Mantel-Haenszel chi-square test. Differences between the high-prednisone and low-prednisone strata with regard to this outcome were compared by logistic regression analysis. The daily prednisone dose, scores on the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire, and the mean serum orosomucoid concentrations were compared by repeated-measures analysis of variance.<sup>27</sup> In these analyses the overall effect of treatment was assessed by comparing trends over time; differences between study groups at the end of follow-up were assessed by comparing the values predicted for the two groups in linear models. The distribution of prednisone use was skewed toward higher daily doses; repeated-measures analysis performed on ranks was used to analyze these data.

The number of patients withdrawn from therapy because of adverse reactions or treatment failure was compared between study groups by Fisher's exact test. The number of adverse events was compared with the use of a Poisson regression model.<sup>28</sup>

We anticipated that 20 percent of the patients receiving placebo would remain in remission. The randomization of 135 patients allowed 80 percent power to detect an absolute difference of 25 percent in this outcome between study groups.

## RESULTS

Between September 1992 and November 1993, 193 patients were assessed to determine whether they were eligible for the study. The most common reasons for exclusion from the study were an inability or unwillingness to give informed consent (10 patients), the presence of risk factors for methotrexate toxicity (8 patients), and a requirement for a contraindicated medication (7 patients). Sixteen patients were excluded for other reasons, leaving a total of 152 eligible patients. Eleven of these patients were not randomized because of a refusal to participate by the patient or the patient's physician (eight patients), an increase in the prednisone dose above 20 mg before randomization (two patients), or the occurrence of a new illness (deep venous thrombosis in one patient). The patients who were eligible but who were not randomized did not differ significantly with respect to age, sex, and duration of disease from the patients who entered the study. Of the 141 study patients, 94 were randomly assigned to receive methotrexate and 47 to receive placebo. Eighty-nine patients (59 assigned to the methotrexate group and 30 to the placebo group) were included in the high-

prednisone stratum, and 52 patients (35 in the methotrexate group and 17 in the placebo group) were included in the low-prednisone stratum. The base-line characteristics of the groups were similar (Table 1).

### Primary Outcome

No patients were lost to follow-up. The same proportion of patients in the two groups (28 percent) was withdrawn from treatment prematurely (26 of 94 receiving methotrexate, as compared with 13 of 47 receiving placebo;  $P=0.99$ ). The proportion of patients withdrawn because of treatment failure was significantly lower in the methotrexate group (7 of 94 receiving methotrexate [7 percent], as compared with 11 of 47 receiving placebo [23 percent];  $P=0.014$ ). After 16 weeks (Fig. 1) the proportion of patients who had discontinued prednisone therapy and remained in remission was higher in the methotrexate group than in the placebo group: 37 of 94 (39 percent) as compared with 9 of 47 (19 percent;  $P=0.025$ ; relative likelihood of entering remission, 1.95; 95 percent confidence interval, 1.09 to 3.48). In the high-prednisone stratum, this outcome occurred in 23 of 59 patients receiving methotrexate (39.0 percent), as compared with 3 of 30 patients receiving placebo (10.0 percent;  $P=0.003$ ; relative likelihood of entering remission, 3.88; 95 percent confidence interval, 1.60 to 9.43). In contrast, 14 of 35 patients receiving methotrexate in the low-prednisone stratum (40 percent) had this primary outcome, as compared with 6 of 17 receiving placebo (35 percent;  $P=0.92$ ; relative likelihood of entering remission, 0.96; 95 percent confidence interval, 0.43 to 2.17). When the percentage of response in the placebo group was subtracted from that in the methotrexate group, the difference in therapeutic gain between the prednisone strata (20 percent in the high-prednisone

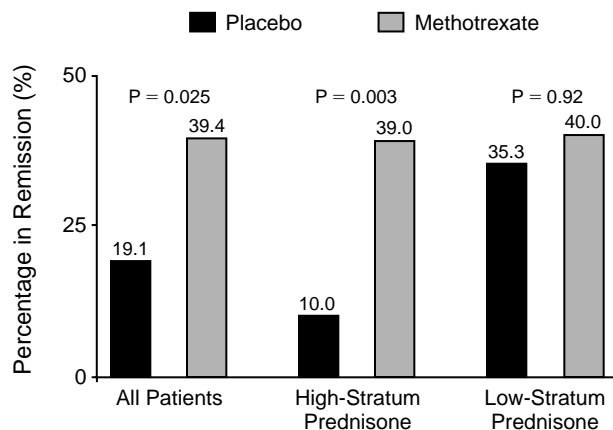


Figure 1. Percentages of Patients in Remission at Week 16, According to Study Group and Stratum of Daily Prednisone Dose before Entry into the Study.

The high-prednisone stratum was receiving a daily dose of more than 20 mg of prednisone, and the low-prednisone stratum a daily dose of 20 mg or less, more than two weeks before randomization. The actual percentages are shown above the bars. P values were derived by the Mantel-Haenszel chi-square test, with adjustment for study center. For the definition of remission, see the Methods section under "Outcome Measures."

stratum minus 5 percent in the low-prednisone stratum) was significant ( $P=0.04$ ).

Characteristics associated with the primary outcome were examined by stepwise logistic regression with the variables of age, sex, prednisone stratum, site of disease, scores on the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire, serum orosomucoid concentration, and smoking status. The base-line score on the Crohn's Disease Activity Index was inversely associated with the probability of discontinuing prednisone and remaining in remission ( $P=0.04$ ; relative likelihood of entering remission, 1.30 for each 50-point decrease in the score on the index). The other characteristics were not significantly associated with the primary outcome.

### Prednisone Use

The patients in the methotrexate group used less prednisone overall than those in the placebo group ( $P=0.026$ ). The difference in prednisone use was detectable in the 90th percentile of the distribution (higher prednisone dose) by week 4 and in the 50th percentile by week 12 (Fig. 2). This difference was due to the increased use of high-dose prednisone therapy in the patients assigned to receive placebo whose condition worsened in the later weeks of the study. The difference was greatest from week 12 through week 16. At the end of the study, the 50th, 75th, and 90th percentiles of the daily prednisone dose in the methotrexate group were 0, 12.5, and 20 mg, respectively, as compared with 5, 20, and 30 mg in the placebo group ( $P=0.003$ ).

### Disease Activity

The average of the mean ( $\pm$ SE) scores on the Crohn's Disease Activity Index (Fig. 3) over the entire follow-up period was significantly lower in the metho-

Table 1. Base-Line Characteristics of the Study Patients.\*

CHARACTERISTIC	METHOTREXATE (N = 94)	PLACEBO (N = 47)
Age — yr	34 $\pm$ 1	36 $\pm$ 2
Male sex	51 (54)	26 (55)
Disease site		
Colon	15 (16)	9 (19)
Small bowel	30 (32)	8 (17)
Both	49 (52)	30 (64)
Months since diagnosis	93 $\pm$ 8	98 $\pm$ 12
Months of continuous disease activity	28 $\pm$ 4	28 $\pm$ 5
Abdominal mass	13 (14)	3 (6)
Previous surgery for Crohn's disease	44 (47)	22 (47)
Cigarette smoker	46 (49)	22 (47)
CDAI score	181 $\pm$ 11	190 $\pm$ 14
IBDQ score	162 $\pm$ 3.4	159 $\pm$ 5.2
Serum orosomucoid concentration — mg/dl†	93 $\pm$ 3.0	95 $\pm$ 5.0
White-cell count — $\times 10^{-9}$ /liter	11.7 $\pm$ 0.3	11.6 $\pm$ 0.5
Hemoglobin — g/liter	135 $\pm$ 1.6	135 $\pm$ 2.6
Platelet count — $\times 10^{-9}$ /liter	367 $\pm$ 11	363 $\pm$ 14

\*Plus-minus values are means  $\pm$ SE, and all other values are numbers of patients followed in parentheses by the percentage of patients in the group.  $P>0.10$  for all paired comparisons between groups. CDAI denotes the Crohn's Disease Activity Index, and IBDQ the Inflammatory Bowel Disease Questionnaire. Higher scores on the CDAI indicate greater disease activity, and higher scores on the IBDQ indicate better quality of life.

†Serum orosomucoid concentrations increase with inflammation. The normal range is 33 to 88 mg per deciliter.

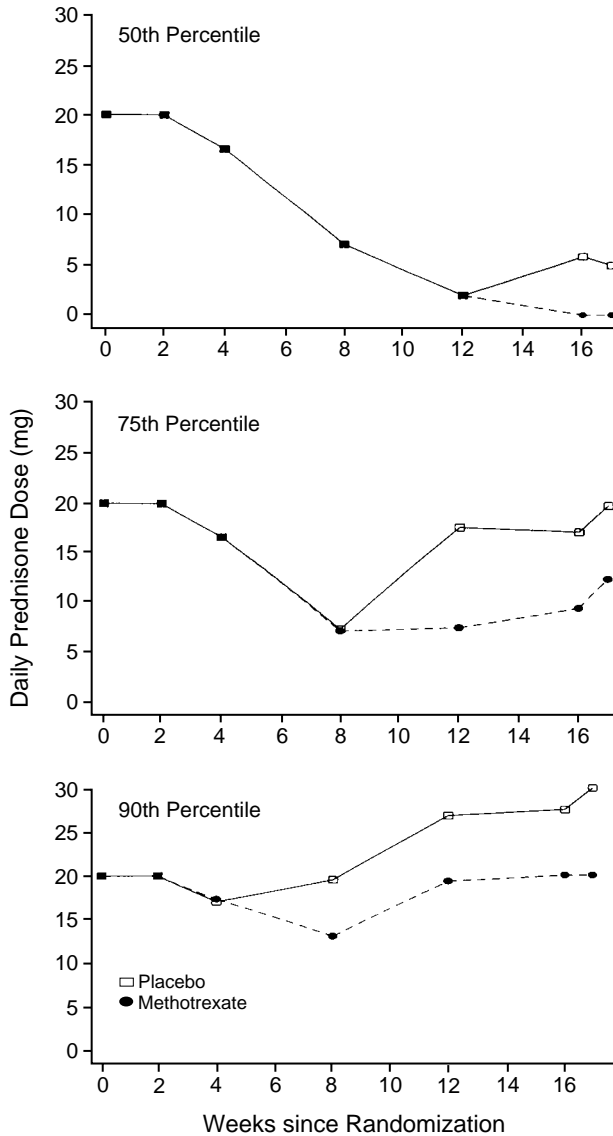


Figure 2. The 50th, 75th, and 90th Percentiles of the Daily Prednisone Dose in the Study Patients, According to Group.

The daily prednisone dose was 20 mg for all patients from week 2 before randomization until week 2 after randomization, when it was tapered by 2.5 mg each week. Patients whose condition improved or remained stable discontinued prednisone therapy at week 12. Patients whose condition worsened at any time during the study were treated with high-dose prednisone (20 to 40 mg daily). The use of higher daily doses in these patients skewed the distribution of prednisone doses toward higher values, making a comparison based on means inappropriate. The overall P value was 0.026 by a repeated-measures log-rank test; the P value at week 16 was 0.003 by the log-rank test.

methotrexate group ( $170 \pm 7$ ) than in the placebo group ( $193 \pm 17$ ,  $P = 0.003$ ). There were significant differences from week 6 onward; at the end of the study, there was a difference of 42 points ( $162 \pm 12$  in the methotrexate group vs.  $204 \pm 17$  in the placebo group,  $P = 0.002$ ).

At base line, the groups' mean quality-of-life scores were similar (methotrexate,  $162 \pm 17$ ; placebo,  $159 \pm 5$ ). After four weeks of therapy, a significant difference between the groups developed (Fig. 3). The average of

the mean quality-of-life scores was higher in the methotrexate group (methotrexate,  $166 \pm 2$ ; placebo,  $155 \pm 3$ ;  $P < 0.001$ ). At 16 weeks the mean values were  $169 \pm 4$  in the methotrexate group and  $151 \pm 6$  in the placebo group ( $P < 0.002$ ). Improvement in quality of life was evident in all four parts of the Inflammatory Bowel Disease Questionnaire ( $P < 0.01$  for all comparisons).

The mean serum orosomucoid concentrations decreased in the methotrexate group and increased in the placebo group (Fig. 3). The average of the mean orosomucoid concentrations in patients treated with methotrexate was  $88 \pm 2$  mg per deciliter, as compared with  $97 \pm 3$  mg per deciliter in patients receiving placebo ( $P = 0.007$ ). There were significant differences between the groups from 4 weeks onward; at 16 weeks, the values were  $82 \pm 3$  in the methotrexate group and  $97 \pm 6$  in the placebo group ( $P = 0.003$ ).

#### Adverse Effects

Among 94 patients treated with methotrexate, 16 (17 percent) withdrew from treatment because of adverse events, as compared with 1 of 47 patients receiving placebo (2 percent,  $P = 0.012$ ). The patient in the placebo group had an episode of polyneuropathy that required hospitalization. The reasons for withdrawal in the methotrexate group were as follows: asymptomatic elevation of serum aminotransferase concentrations (seven patients), nausea (six), skin rash (one), pneumonia probably due to mycoplasma (one), and optic neuritis (one). Table 2 shows the frequency of drug-related adverse events that were not severe enough to warrant discontinuation of the study drug. The patients in the methotrexate group had 2.6 such events per patient, as compared with 2.9 events per patient in the placebo group ( $P = 0.35$ ).

#### DISCUSSION

We found that methotrexate was an effective and well-tolerated treatment for patients with chronically active Crohn's disease. At the time of randomization, the patients had moderately active disease despite receiving 20 mg of prednisone each day. After treatment with methotrexate, significantly more patients were able to discontinue prednisone use than were patients receiving placebo. Because long-term prednisone therapy is associated with a variety of harmful consequences, methotrexate represents an alternative treatment for patients who do not tolerate prednisone or in whom symptoms of Crohn's disease persist despite a moderately high dose of prednisone.

Although they received less prednisone, the patients who received methotrexate had improvement with regard to disease activity and were more likely to enter clinical remission. After 16 weeks of treatment, the mean score on the Crohn's Disease Activity Index ( $162 \pm 12$ ) approximated that in patients with inactive disease ( $\leq 150$ ). Improvement in symptoms as assessed by the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire was detectable by six weeks. This rapid response is in contrast to the relatively slow onset (three to six months) of therapeutic

effect with the antimetabolites azathioprine and mercaptopurine.

There was a significantly greater benefit of treatment in the high-prednisone stratum and in patients with lower scores on the Crohn's Disease Activity Index at base line. It was not, however, our hypothesis before the study that methotrexate would have such a differential effect, and these analyses of subgroups should be interpreted with caution.

Methotrexate treatment appeared to be safe in this group of patients. A previous case report described optic neuritis in association with methotrexate therapy in a patient with psoriasis.<sup>29</sup> Although we believe

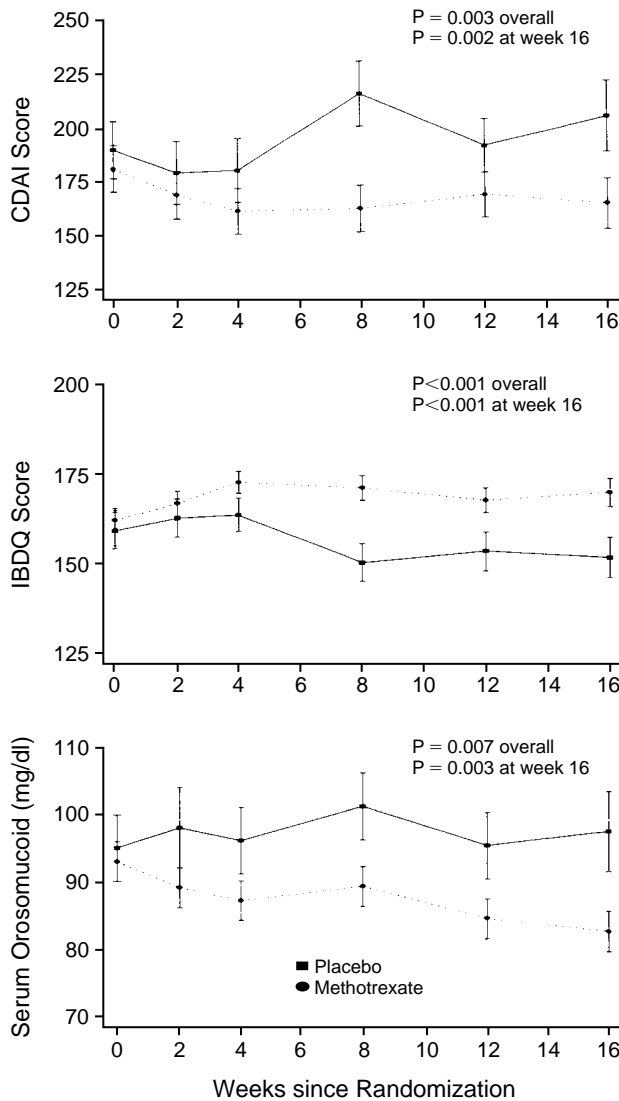


Figure 3. Disease Activity as Assessed by the Crohn's Disease Activity Index (CDAI), the Inflammatory Bowel Disease Questionnaire (IBDQ), and the Serum Orosomucoid Concentration, According to Study Group.

Values are means  $\pm$ SE. Higher scores on the CDAI indicate worse disease; scores of 150 or less are found in patients in remission. Higher scores on the IBDQ indicate better quality of life. P values for the overall comparisons between groups were derived by a repeated-measures analysis of variance; those at 16 weeks were derived by a simple analysis of variance. All analyses were adjusted for base-line values.

Table 2. Adverse Events in the Study Patients According to Group.\*

ADVERSE EVENT	METHOTREXATE (N = 94)	PLACEBO (N = 47)
	<i>no. of patients (% of group)</i>	
Nausea and vomiting	40 (42)	18 (38)
Symptoms of cold	22 (23)	9 (19)
Abdominal pain	17 (18)	12 (26)
Headache	16 (17)	5 (11)
Joint pain or arthralgia	15 (16)	6 (13)
Fatigue	15 (16)	5 (11)
Influenza-like illness	10 (11)	6 (13)
Diarrhea	7 (7)	4 (8)
Abdominal bloating or distension	6 (6)	3 (6)
Skin rash	6 (6)	2 (4)
Insomnia	2 (2)	2 (4)
Other	42 (45)	20 (42)

\*Adverse events related to treatment with the study drug that were not severe enough to warrant discontinuation of the study drug are shown. Patients may have had more than one adverse event.

the occurrence of this complication in one of our patients was probably due to chance, further study of patients with Crohn's disease treated with methotrexate will be needed to exclude a causal relation. The risk of liver disease with long-term methotrexate therapy in patients with Crohn's disease is not known. To minimize the risk of hepatic toxicity, we discontinued treatment if patients had persistently elevated serum aminotransferases, but this may have been unnecessary. It might have been possible, for example, to reduce the dose of medication and follow the patients.<sup>30</sup> However, in the absence of data specific to patients with Crohn's disease, we believe that the recommendations for the use of methotrexate in rheumatoid arthritis should be followed.<sup>31,32</sup> These recommendations include not using the drug in patients with risk factors for hepatic toxicity (alcohol abuse, obesity, or preexisting liver disease), monitoring serum aminotransferase and albumin concentrations at monthly intervals, and performing a liver biopsy in patients with persistent enzyme elevations or hypoalbuminemia. Additional risks associated with methotrexate are those of hypersensitivity pneumonitis,<sup>33</sup> bone marrow depression,<sup>34</sup> and teratogenicity.<sup>35</sup>

Effective drug therapy to maintain clinical remission in patients with Crohn's disease is currently unavailable.<sup>36</sup> Maintenance therapy is a research priority. Budesonide,<sup>37</sup> the new aminosalicylates,<sup>38</sup> and methotrexate should be evaluated in this regard. We are studying the efficacy and safety of 15 mg of methotrexate once weekly for the prevention of relapse of Crohn's disease in patients with quiescent disease.

In conclusion, in our group of patients, methotrexate improved symptoms rapidly and reduced the requirement for prednisone in patients with chronically active Crohn's disease.

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## APPENDIX

The following persons and institutions participated in the North American Crohn's Study Group.

*Steering Committee:* B. Feagan (chair), R.N. Fedorak, G. Greenberg, S. Hanauer, E.J. Irvine, J.W.D. McDonald, J. Rochon, A.H. Steinhart, L. Sutherland, G. Wild, and M. Hopkins. *Adjudication Committee:* B. Feagan, R. Gillies, and J.W.D. McDonald (chair). *Operations Committee:* B. Feagan (chair), J.W.D. McDonald, J. Rochon, and M. Hopkins. *External Advisory Committee:* R. Kozarek, A. Laupacis, J. Singleton, D. Sackett (chair), P. Tugwell, and G. Wells. *Unblinded clinicians:* V. Bain, G. Galler, C. Ghent (chair), E.J. Heathcote, J. Lemaire, G. Sweeney, and C. Watts. *Coordinating center:* L. Cameron, M. Hopkins, E. Seglenicks, and K. Taylor-Dolmer.

*Investigators (listed according to center and number of patients enrolled):* University of Alberta, Edmonton (31) — R.N. Fedorak, T. Alexander, D. Fisher, L. Jewell, P. Kirdeikis, E. Lalor, S. Maciejko, M. Millan, D. Sadowski, E. Semlacher, R. Sherbaniuk, A. Thomson, and B. Yacyshyn; University of Western Ontario, London, Ont. (30) — P. Adams, W. Barnett, M. Belsheim, D. Bondy, R. Eberhard, B. Feagan, P. Gilmore, M. Hopkins, J. Howard, D. Lloyd, J.W.D. McDonald, L. Moyer, T. Ponich, H. Preiksaitis, I. Prokopiw, R. Reynolds, L. Valberg, and W. Watson; McMaster University, Hamilton, Ont. (19) — M. Castelli, S. Collins, K. Croitoru, M. Donnelly, R. Hunt, E.J. Irvine, B. Lumb, D. Morgan, R. Rossman, B. Salena, and T. Seaton; McGill University, Montreal (19) — E. Alpert, D.P. Cleland, D. Daly, M.-C. Dugoua, M. Jabbari, D. Kinneer, M. Lichter, D. Mills, S. Mishkin, P. Mlynaryk, H. Vaupshas, and G. Wild; University of Calgary, Calgary, Alta. (16) — N. Hershfield, K. MacCannell, J. Meddings, L. Price, N. Racicot, E. Shaffer, and L. Sutherland; University of Toronto, Toronto (14) — J. Baker, L. Cohen, G. Greenberg, K. Jeejeebhoy, S. Mikolainis, A. Newman, S. Pearen, F. Saibil, and A.H. Steinhart; University of Chicago, Chicago (12) — I. Hanan, S. Hanauer, P. Schultz, and J. Young.

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