Methotrexate as single therapy in Crohn’s disease: Is its long-term efficacy limited?

Le méthotrexate en monothérapie dans la maladie de Crohn : efficacité limitée à long terme?

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Summary
Objective. — To determine the efficacy and patient tolerance of parenteral methotrexate in the treatment of Crohn’s disease at a dose of 25 mg per week for three months, then at 15—25 mg per week as maintenance therapy.

Patients and methods. — Thirty-five patients (27 women, eight men; mean age 36 years) with steroid-dependent Crohn’s disease were included in the study after failure of azathioprine in 34 cases. Clinical remission was defined as a Harvey–Bradshaw disease-activity index less than or equal to 4 and complete weaning from steroids.

Results. — At the end of the three-month induction treatment, the Harvey–Bradshaw index decreased significantly (4.6 ± 2.9 versus 9.4 ± 5.2; \(P=0.0001\)), as did serum CRP (24 ± 27 versus 43 ± 45 mg/L; \(P=0.01\)) and prednisone dose (5.63 ± 7.3 versus 21.1 ± 18.7 mg/L; \(P=0.00001\)). The mean maintenance dose of methotrexate was 20.3 ± 3.8 mg per week. The rate of clinical remission was 50% at three months and 28% at one year and two years. Nine patients had an adverse event attributed to methotrexate that led to drug withdrawal in six cases (17%).

Conclusion. — Our findings suggest that, for steroid-dependent Crohn’s disease which has failed to respond to thiopurines, long-term methotrexate remains effective in fewer than one in three patients.

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Résumé
But. — Évaluer, au cours de la maladie de Crohn, l’efficacité et la tolérance du méthotrexate parentéral à la dose hebdomadaire de 25 mg pendant trois mois, puis de 15 à 25 mg en traitement d’entretien.

Patients et méthodes. — Trente-cinq patients (27F, huit H, âge moyen 36 ans) et porteurs d’une maladie de Crohn corticodépendante ont été inclus dans l’étude après échec d’un traitement par azathioprine dans 34 cas. La rémission clinique a été définie par un indice de Harvey-Bradshaw inférieur ou égal à 4 et un sevrage complet en corticoïdes.

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Introduction

Evidence for the efficacy of parenteral methotrexate versus placebo for induction of remission and as maintenance therapy for luminal Crohn’s disease has been provided by two randomized studies [1,2]. However, data on its efficacy for fistulizing Crohn’s disease are limited [3–6]. Methotrexate is generally proposed as the second-line treatment for steroid-dependent or refractory forms of Crohn’s disease after failure or intolerance to azathioprine and/or 6-mercaptopurine [7]. In routine practice, relatively few teams have used methotrexate for the treatment of Crohn’s disease [7–9], and its place in the therapeutic armamentarium appears to be declining since the advent of new biological treatments. For example, in a French cohort [10], only 10% of patients with Crohn’s disease were given methotrexate while 15% of them had received the more recently marketed infliximab. There could be several reasons for the diminishing use of methotrexate in Crohn’s patients, including the necessity for parenteral administration, contraindication of pregnancy, risk of adverse events and loss of efficacy over time when using the classical tapering protocol after induction of remission. Feagan et al. [2] evaluated the efficacy of methotrexate at a dose of 15 mg per week to maintain remission induced by a three-month course with a weekly dose of 25 mg. The rates of maintained remission at six months and one year were 85 and 74%, respectively. The results from retrospective series [11–13] appear to be less favorable, with two-year remission rates ranging from 31 to 59%.

The purpose of the present study was to report our experience with methotrexate administered parenterally at an induction dose of 25 mg per week for the first three months, then tapered to 15–25 mg per week, depending on the clinical response.

Patients and methods

Inclusion criteria were as follow:

- patients with steroid-dependent Crohn’s disease treated with methotrexate and managed in an outpatient or inpatient setting by the same physician (PB) between October 1994 and June 2004;
- absence of any contraindication for methotrexate, such as ongoing or desired pregnancy, ongoing infection, chronic liver disease, severe kidney failure, recent history of cancer or known hypersensitivity to methotrexate.

Steroid-dependency was defined as the need for an average steroid dose of 10 mg per day (prednisone equivalent) for three months to maintain disease control [1]. For the first 12 weeks, methotrexate was administered intramuscularly or subcutaneously at a dose of 25 mg per week. After 12 weeks, the methotrexate dose was tapered to 15–20 mg per week, then later increased back up to 20–25 mg per week as needed, depending on disease activity. All patients also received 25–30 mg per week of oral folic acid.

The following patient data were noted on study inclusion: age, gender, smoking habits, disease duration and localization, steroid dose, blood cell counts and results of liver tests, and serum C-reactive protein (CRP). All patients were reviewed one to three months after inclusion, then every six months, to assess methotrexate tolerance and therapeutic efficacy, using the Harvey–Bradshaw disease activity index [14]. Clinical remission was defined as a disease-activity index less than or equal to 4 and a prednisone dose less than or equal to 10 mg per day. Clinical remission and response were determined from data collected in a two- to four-week period prior to the follow-up visit. The need for surgery or infliximab treatment was considered a therapeutic failure even if the methotrexate was not discontinued. Laboratory tests performed every three to six months included blood cell counts, serum CRP and serum ALAT. Endoscopic surveillance was not systematic. The following side-effects were noted prospectively:

- gastrointestinal disorders: abdominal pain, diarrhea, nausea and vomiting;
- infectious disorders;
- liver disorders: persistent elevation of serum ALAT to more than twice the normal level was considered a sign of methotrexate hepatotoxicity;
- hematological disorders: leukopenia, defined as a white cell count less than 4000 per millimetre cube;
- allergic lung disease.

Methotrexate was discontinued in the face of therapeutic failure three months after starting treatment and in the event of a serious adverse event.
Statistical analysis

The clinical-response curve was determined on an intention-to-treat basis using the Kaplan—Meier method. Student’s t test for paired series was applied to compare parametric data: differences were considered significant at P < 0.05. Quantitative data were expressed as means ± standard deviation (SD).

Results

The study cohort included 35 patients (mean age 36 years). Patients’ characteristics at the start of treatment are given in Table 1. Approximately one out of two patients presented with anoperineal lesions; for most of the patients, the main indication for methotrexate was luminal Crohn’s disease. Three patients were given methotrexate after infliximab treatment for anoperineal fistulae, including one low rectovaginal fistula, which closed at the beginning of the methotrexate treatment. All patients except one (with psoriasis) had received azathioprine before the present study. This drug was withdrawn in half of the patients due to intolerance and in the other half because of lack of efficacy.

Thirteen patients were given infliximab during the three months before the start of the present study: nine had only one injection and the remaining four received two or three injections at the dose of 5 mg/kg. Methotrexate was administered at the planned dose of 25 mg per week for the first three months in all patients except five (early methotrexate withdrawal). The dose was then tapered to a mean of 20.3 ± 3.8 mg per week to maintain remission. The mean duration of methotrexate administration was 13.5 ± 14.1 months (range 0.5—57).

After the three-month induction period, disease activity declined significantly, as measured by the Harvey—Bradshaw activity index (4.6 ± 2.9 versus 9.4 ± 5.2; P = 0.0001), as well as CRP level (24 ± 27 versus 43 ± 45 mg/L; P = 0.01) and prednisone dose (5.63 ± 7.3 versus 21.1 ± 18.7 mg per day; P = 0.0001). The rate of clinical remission was 50% at three months, 36% at six months, and 28% at one and two years. The rate of clinical response was 90% at three months, 56% at one year and 51% at two years (Fig. 1). The rates of complete steroid withdrawal at three, six, 12 and 24 months in responders were, respectively: 39, 68, 69 and 100%. Three patients were lost to follow-up. The mid-term rates of clinical remission and clinical response were not significantly different between patients who had received infliximab and those who had not. The rates of clinical remission at three and six months were 46 and 34%, respectively, for patients who had received infliximab, and 54 and 38%, respectively, for those who had not. The efficacy of methotrexate was not statistically different among patients exhibiting azathioprine intolerance (47%, 8/17 patients) or no response (59%, 10/17 patients). No factor predictive of relapse with methotrexate treatment could be identified among methotrexate responders.

The side-effects of methotrexate are listed in Table 2. Nine patients (26%) presented signs of intolerance to methotrexate. The drug was withdrawn because of toxicity in six patients (17%), including one who developed medullary aplasia, as reported elsewhere [15], and discontinued because of suspected hepatotoxicity in three patients, two of whom had signs within the first month of treatment (ALAT elevation two to 10 times greater than normal). One of these patients had a liver biopsy that revealed steatosis. Methotrexate was discontinued in the third patient when the cumulative dose reached 3500 mg because of a persistently elevated ALAT level (1.2 to two times over normal); liver biopsy was not

Table 1 Characteristic features of the patients before treatment with methotrexate.

<table>
<thead>
<tr>
<th>Characteristic feature</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years) (means ± SD; range)</td>
<td>36 ± 17 (16—83)</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>8/27</td>
</tr>
<tr>
<td>Disease duration (months; mean range)</td>
<td>55 (6—228)</td>
</tr>
<tr>
<td>Localization (n (%))</td>
<td></td>
</tr>
<tr>
<td>Ileum—colon</td>
<td>22 (63)</td>
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<tr>
<td>Colon</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Anoperineal</td>
<td>17 (49)</td>
</tr>
<tr>
<td>Prior treatments (n (%))</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>34 (97)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Surgery</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Smokers (n (%))</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Former</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Harvey—Bradshaw disease-activity index (mean ± SD; range)</td>
<td>9.4 ± 5.2 (2—24)</td>
</tr>
<tr>
<td>Prednisone (mg/day) (mean ± SD; range)</td>
<td>21.1 ± 18.7 (0—60)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L) (mean ± SD; range)</td>
<td>43 ± 45 (1—158)</td>
</tr>
</tbody>
</table>

Notes: a Fistulae: eight; fissures: nine.
performed and ALAT level returned to normal after drug withdrawal.

Discussion

The majority of the retrospective studies on the response to methotrexate in Crohn’s disease includes patients with severe, generally steroid-dependent, disease who failed to respond to azathioprine and/or 6-mercaptopurine [11—13,16—18]. Our patients presented similar features — average-dose steroid dependency (approximately 20 mg of prednisone), failure of thiopurines — in all but one case. At three months, the outcome of the 25 mg per week methotrexate regimen — 90% responders — was highly satisfactory, considering the type of patients being treated. Response was defined as a Harvey–Bradshaw index less than or equal to 4 and a prednisone dose less than or equal to 10 mg per day; this latter criterion was well adapted for steroid-dependent Crohn’s disease, defined as the need for prednisone doses more than or equal to 10 mg per day [1]. Clinical remission, which combines clinical response with complete, sustained steroid withdrawal, was only achieved by 50% of our patients. In 37%, methotrexate was administered less than three months after a short regimen of infliximab (one injection in nine of 13 patients). Possibly, the prior infliximab treatment had a positive effect during the first two months of treatment in our patients, but the overall three-month clinical response and remission rates were similar to those from the prospective study reported by Feagan et al. [1], which found a remission rate of about 40% at 16 weeks (using a Best score less than or equal to 150 and steroid withdrawal as the definition of remission). The retrospective studies had three-month outcome criteria similar to ours and remission rates ranging from 20 [13] to 85% [12]. However, in our study, as in the majority of other reports on the topic, remission rates deteriorated rapidly over time, with only 30% of patients still in complete remission after one and two years of methotrexate monotherapy. In the report by Feagan et al. [2], inclusion was limited to responders and to an induction dose of 25 mg per week. In that study, 42% of patients who received a maintenance dose of 15 mg per week had abandoned methotrexate therapy by week 40. In all of the patients but one, treatment was discontinued because of inefficacy. In their retrospective study, Lémann et al. [11] found that only five of the initial 41 patients were still on methotrexate at three years. Dose-tapering beyond the first three months of treatment could be one of the causes of loss of efficacy.

The optimal dose of methotrexate for Crohn’s disease remains a subject of debate. Parenteral administration is probably more effective than oral administration [17,19—21], but data on the appropriate dose for inducing remission and for maintenance therapy remain contradictory. For example, Egan et al. [22] suggested in a prospective study that a 15 mg per week dose was as effective as a 25 mg per week dose for inducing remission; nevertheless, their rate of remission was less than 20% at 16 weeks. As for maintenance therapy, to our knowledge, no prospective study is available comparing different doses of parenteral methotrexate. In many studies, patients relapsing with a weekly dose of 15 mg were tapered up to 20 or 25 mg of methotrexate [2,13,22]. In the controlled trial reported by Feagan et al. [2], 36 patients, including 14 in the methotrexate 15-mg group, relapsed; 61% were given the 25 mg/week dose, which was effective in 50%. Other authors have found no correlation between methotrexate dose and response or remission rate [12]. In our study, despite a mean dose of 20 mg per week, the rate of remission was no higher than previously reported; these results appear to suggest that the loss of efficacy of methotrexate over time is not simply a dose-dependent effect.

The side-effects of methotrexate are relatively infrequent, with rates of 10% reported in Crohn’s patients, and are generally not a reason for treatment withdrawal [23]. In our study, methotrexate was discontinued in 17% of patients because of adverse effects. We found two serious complications: one case of allergic lung disease and one of medullary aplasia. This latter complication in a female patient who had been on methotrexate for two years occurred after taking dipyrone [15]. Liver toxicity was the cause of 50% of the methotrexate withdrawals because of side-effects in our study. It should be noted, however, that early in our study, methotrexate withdrawal was decided in one patient with moderately elevated liver enzymes and evidence of steatosis on a liver biopsy soon after starting treatment, in this case; the methotrexate withdrawal may not have been justified. At present, the risk of methotrexate hepatotoxicity in Crohn’s disease patients is considered low [11,24,25], although standard liver tests may underestimate the hepatic risk associated with methotrexate administration. It is also to be noted that patients with Crohn’s disease are exposed to large cumulative doses of methotrexate. For example, the mean cumulative dose was less than 3 g in the Laharie et al. study [24], where liver toxicity was evaluated with elastometry and biological tests for fibrosis, and in the study by Te et al. [25], where liver biopsy was used.

In conclusion, our findings show that, while the short-term efficacy of methotrexate remains satisfactory, results are less convincing for long-term monotherapy except in a few exceptional cases. Nevertheless, given the retrospective nature of the present study and the small sample size, methotrexate should not be abandoned for patients with Crohn’s disease, particularly since loss of effectiveness is also observed with other therapeutic agents [26]. In addition, a fraction of patients appear to respond favorably to long-term methotrexate therapy, although the characteristic features of these potential responders have not been clearly identified. Lémann et al. [11] suggested that male gender and an isolated ileal or colonic involvement were

<table>
<thead>
<tr>
<th>Table 2 Adverse events in patients treated with methotrexate.</th>
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<tbody>
<tr>
<td>Gastrointestinal disorders: abdominal pain, diarrhea and nausea</td>
</tr>
<tr>
<td>Liver enzymes &gt; twice normal</td>
</tr>
<tr>
<td>Medullary aplasia after combination with dipyrone</td>
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<tr>
<td>Allergic lung disease</td>
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factors favoring response to methotrexate. Furthermore, as in rheumatoid polyarthritis [27], certain studies suggest that methotrexate in combination with infliximab could have a synergistic effect by favoring apoptosis [28] and, thus, prolonging remission through a preventative effect on the development of anti-infliximab antibodies [29,30].

References