Methotrexate in ulcerative colitis: A Spanish multicentric study on clinical use and efficacy

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Abstract

Background: Few data are available on the efficacy of methotrexate (MTX) in ulcerative colitis (UC).
Aim: To evaluate the efficacy and safety of MTX in UC patients.
Patients and methods: UC patients who had been treated with MTX were identified from the databases of 8 Spanish IBD referral hospitals. Patients were included in the study if they received MTX for steroid dependency or steroid refractoriness. Therapeutic success was defined as the absence of UC-related symptoms, complete steroid withdrawal and no requirement of rescue therapies within the first 6 months after starting MTX.
Results: Forty patients were included, 70% treated for steroid dependency and 27% for steroid refractoriness. Thiopurines had been previously attempted in 87.5% of patients. The median dose of MTX used for induction was 25 mg (IIQ 17.5–25) weekly given parenterally in 82.5% of cases.
Eighty-five percent of patients were on steroids when MTX was started. Forty-five percent of patients met criteria for therapeutic success. Initial treatment failures were mainly due to...
1. Introduction

Almost 20% of patients with ulcerative colitis (UC) will require steroid therapy during their lifetime, and up to 60% of those who respond to steroids will become steroid dependent.\(^1,2\) Long-term treatment with thiopurines is widely used in UC as steroid sparing therapy in steroid-dependent patients\(^3\) or for maintenance of cyclosporine-induced remission in steroid refractory cases.\(^4,5\) However, in clinical practice, thiopurines are useful in less than 60% of IBD patients because of lack of efficacy or intolerance.\(^6\) Infliximab has also a steroid sparing effect when administered every 8 weeks for up to 1 year,\(^7\) and it has been shown efficient in small series of steroid-dependent UC patients.\(^8,9\) Nevertheless, infliximab use is associated with loss of response in a proportion of patients,\(^10\) thus limiting its applicability in a long-term setting. Anyway, thiopurines and infliximab are the only recommended drugs for steroid dependent and steroid refractory UC.\(^11\) Colectomy remains as the main alternative for patients failing to thiopurines and/or infliximab, but it entails outstanding drawbacks from the patient's point of view such as a high risk of pouchitis, a decrease in quality of life and infertility.\(^12\)

Methotrexate (MTX) is a potent folic acid antagonist which, at low doses, exhibits anti-inflammatory properties and is therefore used for certain chronic immunological diseases. As far as some RCTs suggest its efficacy in chronically active Crohn's disease,\(^13–15\) this drug is considered as a second-line immunomodulator in these patients.\(^16\) In 1989, Kozarek et al.\(^17\) suggested for the first time that MTX could be useful in inducing clinical remission and reducing steroid requirements in UC patients. However, MTX was not superior to placebo or mesalazine in two early RCTs assessing the efficacy of MTX in chronically active refractory UC.\(^18,19\) Conversely, retrospective and open series suggest that this drug may be useful at least in a proportion of UC patients.\(^17,20,21\)

Given that there is a need for further exploration of new therapies with good safety profile and low cost for these patients, the aim of the present study was to report the clinical use, efficacy, and safety profile of MTX in patients with UC.

2. Patients and methods

UC patients who had been treated with MTX were identified from the IBD databases of eight Spanish referral hospitals. Patients were included in the study if they received MTX for steroid dependency or steroid refractoriness and for maintenance of remission. Patients were followed for at least 6 months unless treatment failure occurred. Only those patients in whom MTX was used concomitantly to anti-TNF agents were excluded. Data were collected retrospectively by case note on a standardized data collection form, including demographic data (age, gender, and smoking habit), and UC clinical data (time from UC diagnosis, disease extent, previous medical treatment, and previous flares). The following parameters related to MTX treatment were accurately assessed: indication, treatment duration, route of administration (oral or parenteral), folic acid supplementation, and steroid therapy at the beginning of MTX.

Therapeutic success was defined as the absence of UC-related symptoms (as judged by the physician), complete steroid withdrawal and no further requirements for systemic steroids or other rescue therapies (cyclosporin, infliximab, or surgery) during the first 6 months after starting MTX. The study was approved by the local Ethics Committee of promoter centre (Hospital Universitari Germans Trias i Pujol).

2.1. Statistical analysis

Results are expressed as median and interquartile range (IQR), or frequencies. Comparison of quantitative and qualitative variables between responders and non-responders was made with the Student-t-test and the \(\chi^2\) test, respectively. Cumulative probability of remaining in clinical remission was calculated by the Kaplan–Meier method. All statistical analyses were performed using the SPSS 12.0 for Windows package (SPSS Inc. Chicago IL, USA).

3. Results

A total of 40 UC patients treated with MTX were identified, accounting only for approximately 1% of all UC patients followed in the participating referral centres. Baseline characteristics of patients are shown in Table 1. Main indications for MTX were steroid dependency (70%) and maintenance of cyclosporine-induced remission (27%). Thiopurine therapy had been previously attempted in 87.5% of patients, resulting in treatment failure or intolerance in similar proportions. MTX was administered parenterally (subcutaneous or intramuscular) at an initial dose of 25 mg weekly in 82.5% for a median 15 weeks (IQR 12–18). Most patients were switched thereafter to a maintenance median weekly dose of 14 mg (IQR 12.5–15), but administered by parenteral route in only 55% of them. Oral folic acid
supplementation (5 mg/weekly) was prescribed together
with MTX in 80% of patients. Eighty-five percent of patients
were on steroids when MTX was started.

At 6 months, 45% of patients (18 out of 40) met criteria for
therapeutic success. Initial treatment failures were mainly
due to inefficacy (11/22, 50%) or intolerance (8/22, 36%). No
differences were found in MTX efficacy regarding previous
failure/intolerance to thiopurines, oral/parenteral route of
administration, or MTX dosage.

Among those patients with initial therapeutic success and
after a median follow-up of 28 months (IQR 22–47), 7 out of
18 required new steroid courses, 4 out of 18 infliximab, and
only 1 was operated on (Fig. 1). In addition, 3 out of these18
patients discontinued MTX beyond 6 months of treatment
because of patient's own volition (1), pregnancy willing (1),
and malaise (1). The cumulative probability of remaining in
rescue-free clinical remission after initial therapeutic
success was 90%, 80%, and 50% at 1, 2, and 3 years,
respectively.

In all, 11 out of 40 patients (27.5%) experienced adverse
effects, leading to MTX discontinuation in eight of them
(Table 2). The most frequent adverse events were malaise
(36%), and hepatotoxicity (27.3%). No cases of pneumonitis,
severe infections, malignancies, or deaths were noticed
during MTX treatment.

### 4. Discussion

Medical therapeutic options in UC patients are limited to
aminosalicylates, steroids, thiopurines, cyclosporine and
infliximab. The present report was intended to know the
real use of MTX and its efficacy in UC patients while waiting
for the results of ongoing randomized, prospective, con-
trolled studies in this setting. To date, two small controlled
trials using low dose, orally administered, MTX in steroid-
dependent UC showed no benefit over placebo or mesala-
zine. Despite these disappointing initial results, several
retrospective or open series reported some efficacy of MTX in
UC, at least in patients intolerant with thiopurines. The
availability of another drug for UC maintenance of remission
is relevant, as far as up to 25% of patients will not benefit
from thiopurines in the long-term because of lack of efficacy
or intolerance, and 13% of patients treated with scheduled
IFX infusions will loss response annually. Finally, in contrast
to thiopurines, MTX use has not been associated with an
increased risk of malignancies in Crohn's disease, being this
an additional advantage for the use of this drug in some
particular clinical settings.

Although a stronger definition for therapeutic success was
used as compared to previous studies that evaluated MTX in
UC, we found that 45% of our patients were in steroid-
free/rescue-free clinical remission 6 months after starting
MTX. This figure is close to those reported in previous studies
in which efficacy rates ranged from 42% to 68%. Interestingly,
among those patients achieving initial therapeutic success
only 22% needed rescue therapy (biologic agents or surgery)
and 38% required a new course of steroids (with no further
rescue therapy) after a median follow-up of 28 months.

### Table 1 Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (23–81)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>67/33</td>
</tr>
<tr>
<td>Smokers</td>
<td>10</td>
</tr>
<tr>
<td>Family history</td>
<td>7.5</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>30</td>
</tr>
<tr>
<td>UC Extent (proctitis/distal/extenses)</td>
<td>5/40/55</td>
</tr>
<tr>
<td>Prior AZA</td>
<td>88.5</td>
</tr>
<tr>
<td>Intolerance</td>
<td>47</td>
</tr>
<tr>
<td>Failure</td>
<td>53</td>
</tr>
<tr>
<td>Time from UC diagnosis to MTX (months)</td>
<td>19 (14–83)</td>
</tr>
</tbody>
</table>

Expressed as median (IQR) or frequencies.

### Table 2 MTX-related side effects.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>n</th>
<th>MTX discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mielotoxicity</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Digestive intolerance</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

FIGURE 1 Individual outcomes of patients.
Some differences between the available RCTs and open or retrospective studies may explain differences in clinical efficacy. First, it has been suggested that the low dose used in controlled studies may have been decisive in their negative results. Of note, MTX proved its efficacy in Crohn's disease using an intramuscular dose of 25 mg/week. However, a small, open study did not find differences in terms of efficacy between 15 mg and 25 mg of MTX in 15 UC patients. Second, another important factor may be the route of administration. Experience in rheumatologic diseases may provide some clues. Studies in rheumatoid arthritis comparing MTX bioavailability when administered parenterally or orally, found a better efficacy when parenteral route was used. In inflammatory bowel diseases, the pharmacokinetic study of low dose oral MTX in a small group of patients showed a good absorption, although therapeutic efficacy was not assessed. To date, data comparing oral vs parenteral MTX in IBD are still lacking, but most studies in Crohn's disease treated with MTX showed better efficacy when using higher doses and parenteral route. In fact, most open series and even two ongoing RCTs evaluating the efficacy of MTX in UC (one from the GETAID and another form the Crohn's and Colitis Foundation of America) mimic the regimen (intramuscular or subcutaneous route, 25 mg/weekly) that was used in the only positive RCT induction study in Crohn's disease. In the present study, no differences in MTX efficacy were found depending on dosage and route of administration, but less than 20% of patients used low, oral, MTX regimen for induction.

In addition to the lack of evidence of MTX efficacy in UC, persistent concerns by gastroenterologists about the safety of long-term use of MTX represent another important limitation for its widespread use. Monitoring bone marrow toxicity and liver function is mandatory in patients receiving MTX. However, a careful selection of patients before starting therapy to rule out those situations that may enhance the risk of hepatotoxicity (such as alcohol abuse, diabetes, obesity, or chronic viral infections) may be even more important. Most studies report side effects leading to discontinuation of MTX treatment in 10–18% of cases, whilst the incidence of mild MTX-related side effects may be as high as 22%. These figures are similar to between 15 mg and 25 mg of MTX in 15 UC patients. Second, a small, open study did not find differences in terms of efficacy when administered parenterally or orally, found a better efficacy when parenteral route was used. In the only positive RCT induction study in Crohn's disease. In the present study, no differences in MTX efficacy were found depending on dosage and route of administration, but less than 20% of patients used low, oral, MTX regimen for induction. In conclusion, MTX could be an effective therapeutic option in UC with a good safety profile and low cost. However, data from ongoing, randomized, controlled studies is urgently needed and additional information to assess the optimal dose, and route of administration is still lacking.

References


