Efficacy, Safety and Mucosal Healing of Methotrexate in a Large Longitudinal Cohort of Inflammatory Bowel Disease Patients

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Keywords

Crohn's disease · Ulcerative colitis · Methotrexate

Abstract

Background/Aims: Evidence for the effectiveness of methotrexate (MTX) in treating inflammatory bowel disease (IBD) is still incomplete. This study assessed the effectiveness, safety and mucosal healing in IBD patients treated with MTX in the Swiss IBD Cohort. **Methods:** Efficacy was defined by physician assessment or by CD activity index <150 points for Crohn's disease (CD) or Modified Truelove and Witts activity index <4 points for ulcerative colitis (UC), measured at least after 3 months of MTX therapy. Mucosal healing was evaluated after 3 months or more of therapy. **Results:** MTX was administered to 341 patients (262 CD; 79 UC) out of 2,660 patients. MTX effectiveness was 59.5% (128/215) in CD and 40.0% (24/60) in UC ($\chi^2 = 7.2409$, $p = 0.007$). Among patients on MTX therapy at the time of analysis, remission was obtained in 87.4% (76/87) and 69.2% (9/13) for CD and UC patients respectively. The median duration of MTX therapy was 40 months for CD and 15 months for UC. Occurrence of adverse events was the first reason for treatment discontinuation (39.4% of all cases). The rate of mucosal healing with

MTX was 9.5% for CD and 25% for UC patients respectively.

Conclusion: MTX therapy was effective for the induction and maintenance therapy in IBD patients, with only a modest mucosal healing ability.

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Introduction

Immunosuppressive agents such as azathioprine (AZA), 6-mercaptopurine and methotrexate (MTX) are used to achieve steroid-free remission and as maintenance therapies in inflammatory bowel disease (IBD) patients [1–3]. MTX use in IBD remains limited, in contrast to its wide use in rheumatic inflammatory disorders [4, 5]. These indications for MTX are based on the results of 2 placebo-controlled trials in Crohn's disease (CD), in which MTX was shown to be effective for the induction and maintenance of clinical remission and to decrease the use of corticosteroid [6, 7]. MTX was mostly prescribed as a second-line immunosuppressive therapy after thiopurines (AZA, 6-mercaptopurine). Limited data on the effectiveness of MTX in clinical practice is available, as the use of the drug is limited. In a recent retro-

spective analysis, MTX had been administered only to 2.1% of patients, despite effectiveness rates, 64.1% in CD patients and 47.8% in ulcerative colitis (UC) patients [8, 9].

MTX is a folate analogue, which binds dihydrofolate reductase and inhibits DNA synthesis resulting in an anti-mitotic action. It also produces an anti-inflammatory action by an increase of adenosine, which decreases pro-inflammatory cytokines production [5]. Its therapeutic effect takes 8–12 weeks to develop [6]. The induction dose in CD is 25 mg/week using a parenteral administration (i.m. or s.c.). A dose of 15 mg/week is used by oral administration (p.o.) for maintenance [1, 3]. MTX side effects are related to the induction of folic acid deficiency [1, 10, 11]. More than 40% of IBD patients experienced side effects, mostly liver and gastro-intestinal toxicity, infections and myelotoxicity [8]. Folate supplementation decreases the rate of these side effects [8].

Mucosal healing is nowadays recognized as an important therapeutic endpoint in CD and in UC, associated with a decreased frequency of disease-associated complications, surgeries and hospitalisations [12–14]. The ability of MTX to induce mucosal healing has not been documented in trials and limited evidence is available from case series, especially in UC. In one recent prospective series, Laharie et al. [15] found that mucosal healing was achieved only in 11% of CD patients treated with MTX, as compared to 50% with AZA and 60% with infliximab (IFX). However, the size of this study, 18 CD patients treated with MTX, limits the value of the observation and no data was obtained in UC.

The aim of the current study is to assess the clinical effectiveness, safety and mucosal healing induced by MTX in a large cohort of CD and UC patients.

Methods

This is a retrospective and longitudinal cohort study conducted in the Swiss IBD Cohort (SIBDC), in which patients diagnosed with CD or UC from all regions of Switzerland have been enrolled since 2005 and are still followed prospectively. For this study, patients with past therapy (before enrolment) or current therapy (at enrolment or during follow-up) with MTX were included. Some patients had therefore 2 courses of MTX. The dose, route of administration and concomitant therapies were recorded. Patients with indeterminate colitis were excluded of this analysis. This study is supported by the Swiss National Science Foundation and was approved by the SIBDC scientific committee as well as by the local ethics committees throughout Switzerland.

Effectiveness was evaluated in 2 different ways for past or current MTX treatment courses. Past treatment efficacy was based on the physician's assessment, as reported in the SIBDC patient enrol-

ment questionnaire after MTX discontinuation. For current therapies, treatment response was defined according to the CD activity index and the UC activity index (Lichtiger score or Modified True-love & Witts activity index) at least after 3 months of MTX therapy [16, 17]. Response was defined with a score under 150 points for CD activity index and 4 points for Modified True-love and Witts activity index. The whole population treated with MTX represents the sum of patients with current and past MTX therapies. Patients with more than one course of therapy were counted only once, as the rate of response did not differ by treatment course in this sub-population.

Safety information about MTX therapy was collected from the enrolment and yearly follow-up SIBDC cohort questionnaires. The type of adverse reactions and their relation to treatment discontinuation were obtained in the enrolment or follow-up cohort questionnaires at the time of MTX discontinuation, as well as by analysis of abnormalities in the laboratory values (haemoglobin, leukocytes, phosphatase alkaline and folate) of patients with a current MTX therapy.

Mucosal healing was defined as an absence of macroscopic lesions observed during colonoscopic evaluation performed at least 3 months after introduction of MTX. A comparison of the rate of mucosal healing between patients with less or more than 3 months of therapy was conducted.

Statistical Analysis

All the data was extracted from the SIBDC database and stored at the SIBDC Datacentre in Lausanne, Switzerland. Statistical analyses were performed using STATA version 12.1 (StataCorp, College Station, TX, USA).

Continuous variables are presented as median, interquartile range and range. Categorical variables are presented as absolute numbers and relative frequencies. Categorical data distribution between 2 or more groups were analysed using the chi-square test or the Fisher's exact test, depending on the sample size. MTX treatment duration was analysed as time-to-event data, and the Kaplan-Meier estimator was used to assess the probability of still being under treatment according to time.

Results

Demographic and Clinical Features of Patients Included

From November 2005 until August 2012, 2,660 patients were enrolled in the SIBDC including 1,508 CD, 1,093 UC and 59 IC, which were excluded. In a total of 2,601 patients, 341 (13.1%) patients were exposed to MTX including 262 (17.4%) with CD and 79 (7.2%) with UC. Among these patients, 231 patients (175 CD, 56 UC) had a past MTX therapy and 153 patients (129 CD, 24 UC) had a current MTX therapy. Thirty-four centres provided cases out of 64 centres participating to the SIBDC (53%). Demographic features of patients at inclusion are listed in Table 1. Montreal classification was used to define the behaviour and location of CD [18].

Table 1. Demographic characteristics of patients at enrolment

Features	CD	UC	Total
Number of patients, %			
Total	262 (76.8)	79 (23.2)	341
Past MTX therapy	175	56	231
Current MTX therapy at inclusion or follow-up	129	24	153
Gender, <i>n</i> (%)			
Male	111 (42.4)	46 (58.2)	157 (46)
Female	151 (57.6)	33 (41.8)	184 (54)
Age at diagnosis, years, median (range)	26 (6–81)	31 (13–67)	27 (6–81)
Smokers (<i>n</i> = 333; CD = 257/UC = 76)	117 (45.5)	9 (11.8)	126 (37.8)
Behaviour of CD, <i>n</i> (%)			
Inflammatory (B1)	111 (42.4)	–	–
Stricturing (B2)	54 (20.6)	–	–
Penetrating (B3)	97 (37.0)	–	–
Perianal	69 (26.3)	–	–
Location, <i>n</i> (%)			
Ileal (L1)	88 (33.6)	–	–
Colonic (L2)	75 (28.6)	–	–
Ileocolonic (L3)	89 (34.0)	–	–
Upper digestive tract (only) (L4)	3 (1.1)	–	–
Other/unknown	7 (2.7)	–	–
Pancolitis	–	39 (49.4)	–
Left colitis	–	33 (41.8)	–
Proctitis	–	6 (7.6)	–
Other	–	1 (1.3)	–

Baselines features of all 153 patients (129 CD, 24 UC) with a current MTX therapy at inclusion or during follow-up in the SIBDC are shown in Table 2. Patients with only a past therapy at enrolment are not included in this table, as precise disease phenotype at the time of MTX therapy could not be determined retrospectively in the database. MTX was prescribed as a monotherapy in 27.1% CD patients and in only one UC patient. Concomitant steroid therapy was observed in 27.9% of CD patients and in 50.0% of UC patients. MTX was used as a first-line therapy before thiopurines in 28.1% of IBD patients.

Clinical Effectiveness of MTX

In the whole exposed population, effectiveness of MTX was significantly higher in CD than in UC, with a rate of response of 59.5% (128/215) for CD, as compared to 40.0% (24/60) in UC ($\chi^2 = 7.2409$, $p = 0.007$; Table 3). Smoking status was not found to affect the response rate in CD.

For patients with current MTX therapies, the effectiveness of MTX in CD was not significantly lower as compared in UC, with a rate of response of 87.4% (76/87) for CD, as compared to 69.2% (9/13) in UC ($\chi^2 = 2.9143$, $p = 0.088$, Fischer's exact test 0.103; Table 3). Patients with

an MTX therapy of less than 3 months or without a complete activity index assessment could not be evaluated (42 CD and 11 UC).

MTX past therapies could be evaluated only in 206 patients (156 CD, 50 UC) out of 231 patients (175 CD, 56 UC). Out of 156 CD patients, 77 (49.4%) has a past therapy evaluated as a response. The rate of response was not significantly lower in UC with a rate of 34.0% (17/50) ($\chi^2 = 3.6003$, $p = 0.058$).

Time on Therapy with MTX

The probabilities for patients with CD or UC to remain on MTX therapy, regardless of the reasons of discontinuation, are shown in a Kaplan-Meier estimator for 111 IBD patients (94 CD, 17 UC) with a current therapy (Fig. 1). After 15 months, 75% of CD patients remained on MTX therapy, a value which is 50% for UC patients, and after 40 months, only 50% of CD and 25% of UC are still on MTX therapy. The median treatment duration was 12 months (Table 2), which is a duration long enough to assess response, as MTX typically takes 8–12 weeks to develop effect. However, as the SIBDC only performs a yearly follow-up, our data is not suitable to precisely define time-to-response.

Table 2. Characteristics of patients with current MTX treatment

Features	CD	UC	Total
Number of patients	129	24	153
Duration of MTX, months, median (IQR, range), <i>n</i> = 140 (CD = 118/UC = 22)	13 (1–36, 0–108)	5.5 (1–22, 0–78)	12 (1–36, 0–108)
Way of MTX's administration, <i>n</i> (%), <i>n</i> = 150 (CD = 126/UC = 24)			
Subcutaneous	94 (74.6)	18 (75.0)	112 (74.7)
Per os	32 (25.4)	6 (25.0)	38 (25.3)
MTX dose, mg/week, median (IQR, range), <i>n</i> = 151 (CD = 128/UC = 23)	15.0 (15–20, 3.6–30)	15.0 (12.5–25, 2.5–25)	15.0 (15–20, 2.5–30)
Folic acid supplementation, <i>n</i> (%)	83 (64.3)	14 (58.3)	97 (63.4)
Treatments associated with MTX, <i>n</i> (%)			
Salicylates	12 (9.3)	18 (75.0)	30 (19.6)
Antibiotics	3 (2.3)	0 (0.0)	3 (2.0)
Calcineurin inhibitors	0 (0.0)	2 (8.3)	2 (1.3)
Thiopurines	3 (2.3)	0 (0.0)	3 (2.0)
Anti-TNFs	38 (29.5)	6 (25.0)	44 (28.8)
Steroids	36 (27.9)	12 (50.0)	48 (31.4)
Others	12 (9.3)	1 (4.2)	13 (8.5)
None (MTX monotherapy)	35 (27.1)	1 (4.2)	36 (23.5)
Treatments before MTX, <i>n</i> (%)			
Salicylates	57 (44.2)	14 (58.3)	71 (46.4)
Antibiotics	66 (51.1)	8 (33.3)	74 (48.4)
Calcineurin inhibitors	1 (0.8)	2 (8.3)	3 (2.0)
Thiopurines	92 (71.3)	18 (75.0)	110 (71.9)
Anti-TNFs	42 (32.6)	8 (33.3)	50 (32.7)
Steroids	89 (69.0)	13 (54.2)	102 (66.7)
Others	12 (9.3)	0 (0.0)	12 (7.8)

Table 3. MTX therapy efficacy for CD and UC

Therapy	Effect	CD		UC		Total	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Total	Response	128	59.5	24	40.0	152	55.3
	Non-response	87	40.5	36	60.0	123	44.7
	Total	215	100.0	60	100.0	275	100.0
Current	Response	76	87.4	9	69.2	85	85.0
	Non-response	11	12.6	4	30.8	15	15.0
	Total	87	100.0	13	100.0	100	100.0

Safety of MTX

As side effects were recorded at the time of MTX discontinuation, no data is available about side effects that did not lead to treatment discontinuation. Therefore, only 91 patients were included in this analysis. The prevalence of side effects was the first reason for MTX discon-

tinuation in 39.4% (91/231) of cases, 40.0% for CD (70/175) and 37.5% for UC (21/56). Details of side effects were reported only for 52 out of 91 patients with side effects by the physicians (39 CD, 13 UC; Table 4). The most frequent side effect was gastrointestinal intolerance in 38.5% patients (43.6% of CD, 23.1% of UC).

Table 4. MTX side effects (SE) in the order of frequency

SE	CD		UC		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Patients with reported type of SE	39	100	13	100	52	100
Gastrointestinal intolerance	17	43.6	3	23.1	20	38.5
Liver cirrhosis/fibrosis	5	12.8	1	7.7	6	11.5
Hypersensitivity reactions	3	7.7	1	7.7	4	7.7
Stomatitis/mucositis	3	7.7	0	0.0	3	5.8
Opportunistic infections	2	5.1	1	7.7	3	5.8
Abdominal pain/diarrhea	1	2.6	2	15.4	3	5.8
Cough/pneumonitis	1	2.6	1	7.7	2	3.8
Leucopenia/thrombopenia	1	2.6	0	0.0	1	1.9
Others	8	20.5	4	30.8	12	23.1

Fig. 1. Kaplan-Meier curves of survival probability to remain on MTX therapy for patients with CD and UC.

The abnormalities in the last laboratory values of patients on current MTX therapy were leucopenia in 4/141 patients (3/119 CD, 1/22 UC), anemia in 16/141 (13/119 CD, 3/22 UC), elevated alkaline phosphatase in 4/109 (4/91 CD, 0/18 UC) and low folate values in 10/67 (8/45 CD, 2/12 UC).

Mucosal Healing

Mucosal healing was observed in 11.8% (6/51) CD patients with less than 3 months of MTX therapy and in 9.5% (4/42) of patients treated for more than 3 months.

In contrast, in UC patients, mucosal healing was not observed (0/7) in patients treated for less than 3 months with MTX, while it was reported in 2 out of 8 patients treated for more than 3 months.

Discussion

This retrospective and longitudinal study assessed the safety, clinical effectiveness and mucosal healing induced by MTX in a large unselected cohort of CD and UC pa-

tients. The rate of use of MTX in the SIBDC was 13.1%, which is higher than previously published [8]. This rate was higher for CD (17.4%) than for UC (7.2%). MTX efficacy has been long established in randomised trials for CD, but only recently in UC [19]. It is not surprising, therefore, that in a retrospective and longitudinal study, the rate of use of MTX in both diseases has followed evidence-based medicine, with higher use in CD [6, 7]. In most cases, MTX was a second-line immunosuppressive therapy after thiopurines, which is in agreement with the prior observations [8]. Furthermore, in our study MTX was rarely used as a monotherapy (Table 2). Interestingly, about one third of patients received MTX after anti-TNF failure, which illustrates a potential use of this compound.

Effectiveness

In the whole population of this study, MTX efficacy was evaluated at 59.5% for CD and at 40.0% for UC (Table 3), which corresponds to the rate measured in another study that tested a smaller group of patients [8, 20–22]. To our knowledge, the size of the group in the SIBDC represented the larger study ever done which assessed MTX efficacy in IBD patients.

The rate of effectiveness of past MTX therapies was lower than the rate of current therapies (Table 3). This is not surprising in a longitudinal study, as the likelihood of pursuing an effective therapy should obviously be higher than that of pursuing past therapies, which include all the cases with adverse reactions or other causes of treatment discontinuation, especially the wish to conceive a family. Furthermore, effectiveness was assessed in 2 different ways with a past (on the physician's assessment retrospectively) or a current therapy (according to the IBD activity index), which may also affect the results.

The probability for patients with CD or UC to remain on MTX therapy was higher for CD than UC (Fig. 1). The lower effectiveness in UC can partially explain the higher rate of discontinuation of MTX in this condition, as compared to CD. However, the lack of randomized trial to provide a proof of efficacy of MTX in UC probably also influences physicians and patients, leading to the early termination of treatment. This situation may soon change with the full publication of the METEOR study [19]. Another explanation could be that MTX was less effective in UC than in CD, or that the low mucosal healing rate, which is easier to monitor in UC than in CD, also influenced the decision to maintain the patients under therapy. Furthermore, in this study, MTX was a treatment used in the medium term and not in long term, as shown by

the 12-month median duration of current therapies (Table 2). The reason for treatment interruption after established maintenance therapy was a progressive loss of efficacy, observation that confirms the findings of another study [23]. However, a small proportion of patients, in particular with CD, seem to benefit of MTX therapy in the long term.

Safety

In our study, side effects were the first reason for discontinuation of MTX therapy, at a rate which compares to rates reported previously [8, 21, 22]. Most side effects were benign, like gastrointestinal intolerance (Table 4). Liver cirrhosis/fibrosis was reported by physicians in 11.5% as the reason for MTX discontinuation. However, only a few patients had abnormalities only in the liver laboratory value collected, which was alkaline phosphatase (in the SIBDC, the original aim was to detect patients with primary sclerosing cholangitis). The use of alkaline phosphatase as a marker of MTX-linked hepatic toxicity is certainly not very sensitive, and could thus have induced an underestimation of the rate of liver intolerance in this patient population. Infections and opportunistic infections (3/52 patients, 5.8% of side effects) and leucopenia (4/141 patients, 2.8%) were uncommon, with lower rates than those reported with other immunosuppressive therapies. Indeed, in some studies, the rate of leucopenia with thiopurines was established between 2.2 and 15% [24, 25]. In his retrospective study, Toruner et al. [25] calculated a risk of opportunistic infection significantly increased with the use of corticosteroids (OR 3.3), thiopurines (OR 3.8) or IFX (OR 4.4), but was not significantly increased with a treatment of MTX or mesalazine. Our study confirms that MTX can probably be considered a relatively safe therapy with respect to infectious complications, in comparison to other immunosuppressive therapies for IBD patients. However, because of the high rate of discontinuation due to side effects, patients under MTX should be vaccinated as recommended and carefully monitored for infection [26].

Our study highlighted that folic acid supplements were not prescribed systematically with MTX among SIBDC patients (Table 2), while its systematic use is recommended [1], as folic acid decreases the rate of side effects occurrence [8]. This low rate of use in comparison to other studies could contribute to the high rate of discontinuation due to side effects observed in our study. In the absence of a strict time correlation of the available information regarding prior therapies in the SIBDC da-

tabase, a statistical analysis of the correlation between the occurrence of side effects and lack of acid folic supplements could however not be conducted.

Mucosal Healing

In our study, mucosal healing with MTX was considered possibly associated with MTX only when measured after at least 3 months of therapy. Only a small proportion of CD patients achieved a complete mucosal healing, which corresponds to the results of another study [15]. For UC, 2 patients achieved mucosal healing but the population was composed only of 8 patients. The rate of healing was stable for CD and not for UC when comparing assessments with treatment duration of less and more than 3 months. With the limitations associated with this very limited dataset, the efficacy of mucosal healing seemed to be earlier for CD than for UC, and lower as compared to the mucosal healing rates achieved with AZA or IFX [15].

Limitations

Some methodological limitations can be identified in the present study. First, the results were assessed with different parameters, depending whether MTX therapy was current or only described in the patient's past medical history, making patients not strictly comparable for some study endpoints. Second, the follow-up of patients was performed only once a year, limiting the collection of intercurrent events in the follow-up, such as short relapses or time limited side effects, which may be prone to recollection bias. Third, the yearly follow-up also implies that some information may be missing to fully understand medical decisions, like the reasons for treatment discontinuation. Finally, the yearly response rate measured with an activity index once a year is far from being precise. However, despite these limitations, the SIBDC provides one of the more precise follow-up of longitudinal cohorts, with the overall physician decisions and current therapies precisely collected, making the actual treatment rates valid.

Conclusion

This retrospective and longitudinal study suggests that MTX is a useful therapy for IBD, in particular for CD, with a treatment duration that extends beyond one year, which is comparable to other therapies. In UC, MTX showed an effectiveness that compares to CD, but therapy is often of shorter duration. Mucosal healing with MTX for both IBD indications was low.

The real potential of MTX in IBD is still poorly evaluated, and the results of the first randomized trial testing MTX against placebo in UC are awaited. Because this treatment is cheap, well tolerated and associated with a low risk of opportunistic infections, further studies evaluating its potential in combination therapy with biological therapies, including anti-TNF and anti-integrin antibodies should be encouraged.

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The manuscript, including related data, figures and tables has not been previously published and the manuscript is not under consideration in another journal or book.

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