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# Use of methotrexate in patients with inflammatory bowel diseases

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## ABSTRACT

*Methotrexate (MTX) is one of the immunosuppressants commonly used in inflammatory bowel diseases. There is very good evidence for its use in patients with steroid-dependent or steroid-refractory Crohn's disease for induction as well as maintenance of remission. Optimal dose as well as mode of application is still a matter of debate. The only large randomised controlled trials used 25mg/wk for induction and 15 to 25mg/wk for maintenance of remission, both applied intramuscularly. Current guidelines recommend methotrexate in patients with extensive disease, steroid-refractory, and steroid-dependent disease. They even suggest MTX for patients with infrequent relapses in the need of repetitive corticosteroid therapy. In clinical practice it is mainly used in patients who failed treatment with thiopurines (azathioprine or 6-mercaptopurine) or who are intolerant to these drugs. MTX can also be used in paediatric patients, whereas the evidence for its effectiveness in fistulising disease is very weak. Two small studies did not prove that MTX is efficacious in ulcerative colitis. Even though case series suggest otherwise, its use is not recommended by current guidelines for patients with ulcerative colitis.*

## Introduction

Inflammatory bowel diseases (IBD), namely Crohn's disease and ulcerative colitis are characterised by a mostly relmitting-relapsing disease course. Treatment for IBD varies whether it is for induction of remission during an acute relapse or whether it is for maintenance of remission. The most effective drug for the short-term treatment of disease flare-ups are still glucocorticoids since they lead to clinical remission in 54–92% of all cases (1, 2). Unfortunately out of the Crohn's disease patients who need corticosteroid treatment, only

32% have a prolonged response. The same holds true for 49% of ulcerative colitis patients (2). Also low-dose glucocorticoids are not able to prevent relapses (3-5). Therefore other immunosuppressive drugs are being used in order to not only induce but also maintain remission in these patients.

Methotrexate (MTX) is one of the immunosuppressants commonly used in IBD. In Crohn's disease the effectiveness of MTX is well shown. For ulcerative colitis the evidence is less clear. Furthermore there are still open questions about the optimal dose and administration. The latter could be especially important in IBD patients, who very often show signs of malabsorption.

## Crohn's disease

In luminal Crohn's disease MTX is effective for induction and maintenance of remission based on two trials. The only large high quality randomised controlled trial on the treatment of active Crohn's disease with MTX was performed by the North American Crohn's Study Group Investigators. The study included patients who were steroid-refractory or -dependent. These patients were given MTX 25mg/wk or placebo intramuscularly for 16 weeks. Patients with risk factors for liver disease were excluded from the study. Thirty-seven out of ninety-four patients (39%) in the MTX group and 9/47 patients (19%) in the placebo group entered remission and discontinued prednisone ( $p=0.025$ ). Patients in the treatment group had a statistically significant lower prednisone dose, a lower Crohn's disease activity index and higher disease specific quality of life as measured by the inflammatory bowel diseases questionnaire (6).

In an extension to their study about induction of remission the same group investigated the effect of MTX on the maintenance of remission in patients,

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who had entered steroid-free remission with MTX. Again MTX or placebo was given intramuscularly, this time at a dose of 15mg/wk. After 40 weeks 26/40 patients (65%) in the treatment group and 14/36 patients (39%) in the placebo group had remained in remission ( $p=0.01$ ). Secondary outcome parameters were also in favour of MTX: Patients in the treatment group needed less often steroid treatment. Also of the 36 patients who relapsed 22 were subsequently re-treated with 25mg/wk MTX. Twelve out of those 22 (55%) were able to discontinue the steroids by week 40 compared to 2/14 patients (14%) who did not receive MTX (7).

The studies by the North American Crohn's Study Group Investigators clearly indicate that parenteral MTX at 25mg/wk is efficacious for induction of remission in patients with active steroid-dependent or steroid-refractory Crohn's disease. While most patients can maintain remission with only 15mg/wk some might need higher doses. Several case series were able to reproduce the results of these two trials using similar doses and route of application proving its effectiveness in clinical practice (8).

Aside from these two large trials investigating relatively high doses of parenteral MTX several smaller trials also tried to investigate the efficacy of MTX in Crohn's disease using mostly lower doses and oral application, which would be easier and probably less toxic.

Arora *et al.* included 33 patients and used between 15 and 22.5mg/wk of oral MTX. The study was not able to show a difference between MTX and placebo. Treatment failure occurred in 11/15 (73%) of patients treated with MTX and 15/18 (83%) of patients treated with placebo ( $p=0.48$ ) (9). Oren *et al.* compared only 12.5mg/wk of oral MTX to a low dosage of 6-mercaptopurine (6-MP) (50mg/d) and placebo respectively. The proportion of patients entering remission within nine months was the same in all three study arms (MTX: 10/26, 38%; 6-MP: 13/36, 41%; placebo: 12/26, 46%;  $p>0.05$ ) (10). Two more studies tried to compare MTX to thiopurines. Ardizzone *et*

*al.* compared 25mg/wk of intravenous MTX to a standard dose of azathioprine (2.0mg/kg body weight). Again the study could not detect a difference between azathioprine and MTX with 17/27 (63%) of patients in the azathioprine group and 15/27 (56%) of patients in the MTX group being in remission after 6 months ( $p=0.39$ ) (11). All three of these studies were inconclusive. This could be attributed to lower effectiveness of oral or smaller doses as well as the low number of subjects in each of these trials. Maté-Jiménez *et al.* investigated a mixed population of patients with Crohn's disease or ulcerative colitis, who were randomised to treatment with 15mg/wk of oral MTX, a standard dose of 6-MP (1.5mg/kg body weight), or mesalazine. While the patients were randomised together, they were analysed separately. Among the 38 patients with Crohn's disease more patients treated with MTX were in remission after 30 weeks as compared to patients treated with mesalazine (58% vs. 25%,  $p<0.01$ ). Due to its small size this study did not provide conclusive results though, when comparing MTX to 6-MP (12).

The trials differed markedly with respect to the comparator, dose, application and outcome evaluation. However, they did have in common that they all included only a small number of patients, so it is difficult to draw a final conclusion about the feasibility of lower doses and oral application from these mostly negative studies. Taken together the available evidence firmly supports the use of 25mg/wk of parenteral MTX for the induction of remission. Oral bioavailability of MTX in patients with IBD has been tested in several studies. It does not seem to be any different from patients with rheumatoid arthritis (13-15). This issue will be discussed in more detail in another article in this issue. Nevertheless no clinical study was able to prove the efficacy of oral MTX in IBD so far.

In rheumatoid arthritis infliximab is mostly given together with MTX. Hence two more trials compared MTX to placebo when given in combination with infliximab. Schröder *et al.* investigated 19 patients and added MTX to

an induction scheme of infliximab of 5mg/kg body weight given at weeks 0, 2, and 6. The groups in this small study did not differ with respect to the proportion of patients in remission at the end of this induction phase (16). A larger trial so far has only been reported in abstract form. Feagan *et al.* included 126 patients who were either treated with an induction scheme of infliximab followed by infliximab every eight weeks or infliximab plus 25 mg/wk subcutaneous MTX. The study was not able to prove a difference between the two groups. By week 50, 31% of patients in the MTX group had failed treatment compared with 30% of those assigned to placebo ( $p=0.63$ ) (14). If anything the additional advantage of methotrexate seems to be rather small with a 95%-confidence interval of about 11% around the remission rate of 69%. The additional effect of azathioprine on the other hand in combination with infliximab has also been shown to be in the range of 11% to 16% after one year (17).

There is a continuing debate whether mucosal healing might be superior to clinical remission as a predictor of the long-term course in Crohn's disease. However, only small reports are available on the ability of MTX to induce mucosal healing. In these four studies involving between 8 and 18 patients the percentage of patients who showed mucosal healing varied from 11 to 38% (18-21). This would be slightly worse than the reported figures for infliximab or azathioprine (22).

#### Children and adolescents

No controlled trials have been performed in children. Several case series suggest that MTX is equally effective in this population (Table I). Two studies only report response and not complete remission (23, 24). The other three studies included a total of 131 children and adolescents with Crohn's disease. All patients had been treated unsuccessfully with thiopurines. In some cases MTX was initiated after failure of infliximab treatment too. After 6 months remission rate varied from 49% to 77%, after 12 months from 36% to 53% (25-27).

**Table I.** Case series on MTX in paediatric Crohn's disease patients.

	Response	Remission after 6 months	Remission after 12 months
Mack 1998		10/14 (77%)	4/14 (36%)
Uhlen 2006	49/61 (80%)	30/61 (49%)	28/61 (46%)
Ravikumara 2007	7/10 (70%)		
Turner 2007		37/60 (62%)	32/60 (53%)
Weiss 2009	18/24 (75%)		

**Table II.** Case series on MTX in fistulising Crohn's disease.

	Mean observation time (range)	Complete response	Partial response
Baron 1993	18 weeks	0/1	0/1
Lémann 1996		2/4	
Mahadevan 2003	17 (2–51) months	4/16	5/16
Soon 2004	6 months	4/18	4/18

**Table III.** Case series on higher doses of MTX in ulcerative colitis.

	Median observation time (range)	Remission	Response
Kozarek 1989	12 weeks	2/7 (29%)	5/7 (71%)
Kozarek 1992	12 weeks		21/30 (70%)
Siveke 2003		4/4 (100%)	4/4 (100%)
Cummings 2005	7 (2–90) months	21/50 (42%)	36/50 (72%)
Rook 2005	mean: 10 (4–18) months	6/8 (75%)	
Nathan 2008	15 (3–37) months	11/23 (48%)	14/23 (61%)
Wahed 2009	6 months		22/32 (68%)

### Fistulising disease

The evidence for using MTX in fistulising disease is very weak; the few available case series do not suggest a very high effectiveness. Two case series specifically assessing the effectiveness of MTX in fistulising disease have been published. Two other case series also report on the effectiveness of MTX for the treatment of fistulas (28–31). The results of these studies are summarised in Table II.

### Clinical practice guidelines

The current clinical practice guidelines by the European Crohn's and Colitis Organisation (ECCO) recommend immunosuppressants for all patients with extensive disease, with steroid-refractory and steroid-dependent disease. They even suggest its use in patients with infrequent relapses in the need of repetitive corticosteroid therapy (32). For all these indications methotrexate is mentioned side by side with the

more commonly used thiopurines (azathioprine or 6-MP). Also methotrexate is recommended for patients who are intolerant to thiopurines or failed thiopurines. While using methotrexate is equally recommended in paediatric patients it is only considered useful in fistulising disease after all other treatment options including anti-TNF- $\alpha$  blockers have failed.

The recommended dose for induction of remission is 25mg/wk. For maintenance of remission the guideline recommends no less than 15mg/wk.

### Ulcerative colitis

While the effectiveness of MTX in Crohn's disease is well shown, so far there is no definite clinical trial that proves efficacy in ulcerative colitis. Similar to their study in Crohn's disease Oren *et al.* investigated the use of 12.5mg/wk oral MTX in 67 steroid-dependent or -refractory patients. There was no difference in the primary

outcome: 18/25 (49%) of patients in the placebo group and 14/23 (47%) in the MTX group went into remission at some point in the first nine months ( $p=0.87$ ). None of the secondary endpoints showed clear superiority of MTX either (33). As mentioned above Maté-Jiménez included a mixed population of IBD patients in their study. Steroid-dependent patients were treated either with 15mg/wk oral MTX, a typical dose of 6-MP (1.5mg/kg body weight), or mesalazine. Among the patients with ulcerative colitis 79% in the 6-MP group, 58% in the MTX group, and 25% in the mesalazine group were in remission after 30 weeks. While 6-MP turned out to be superior to mesalazine in these patients ( $p<0.05$ ), MTX did not ( $p=0.20$ ) (12).

Just like in most Crohn's disease studies both these controlled studies were done with a relatively low dose of oral MTX. Considering that the only positive trial in Crohn's disease used a higher dose of parenteral MTX one might argue that MTX is only effective at 25mg/wk in active ulcerative colitis. Most case series were indeed done with this dose. Out of the ten studies, seven reported response or remission rate in ulcerative colitis patients (see Table III) (18, 34–39). Those case series suggest that MTX might be effective in ulcerative colitis at higher doses. Two clinical trials are underway to finally answer this question. The French/European METEOR trial is not expected to be finished before 2011, while the US MERIT-UC trial is currently in preparation.

Accordingly, the current European clinical practice guidelines on ulcerative colitis recommend MTX neither for induction nor for maintenance of remission (32).

### Side effects in IBD patients

Several case series suggest the side effect profile of MTX seems in patients with IBD seems to be similar to patients with rheumatoid arthritis. The frequency of clinically significant liver disease in patients with Crohn's disease taking MTX is still unclear. So far only one small study systematically investigated this issue in inflammatory bowel diseases. Out of 32 patients with cumula-



tive MTX doses >1500mg, 20 patients underwent liver biopsies as recommended for MTX-treated patients with psoriasis. One patient had hepatic fibrosis. This patient had received a cumulative dose of 1650mg MTX and he had multiple risk factors (obesity, diabetes, other potentially hepatotoxic drugs) (40). Hence the risk for liver fibrosis in IBD patients generally seems to be lower than for patients with psoriasis so more relaxed surveillance regimens as for instance applied in rheumatoid arthritis are more feasible.

### Summary

MTX is proven effective in patients with Crohn's disease for induction of remission in active disease as well as long-term maintenance of remission. The typical dose for induction of remission is 25mg/wk parenterally. After induction of remission, which can take more than three months, the dose is usually reduced to about 15mg/wk. Some authors favour the oral application in quiescent disease. The evidence for MTX is weaker than for azathioprine or anti-TNF-alpha antibodies, so MTX is rarely used as the first agent in steroid-dependent or steroid-refractory patients. An exception might be patients with dominant peripheral arthritis as an extra-intestinal manifestation. Typically in clinical practice MTX is used in patients, where azathioprine had to be discontinued because of side effects as an alternative immunosuppressant. A similar approach is used in paediatric patients or patients with perianal fistulising disease even though only case series are available to guide that decision.

For patients with ulcerative colitis, no controlled trial was able to prove that MTX is efficacious in this population. Even though all these trials were small and hampered by the fact that none of them used high doses of parenteral MTX, results from ongoing trials have to be awaited before MTX can be recommended in the treatment of ulcerative colitis.

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