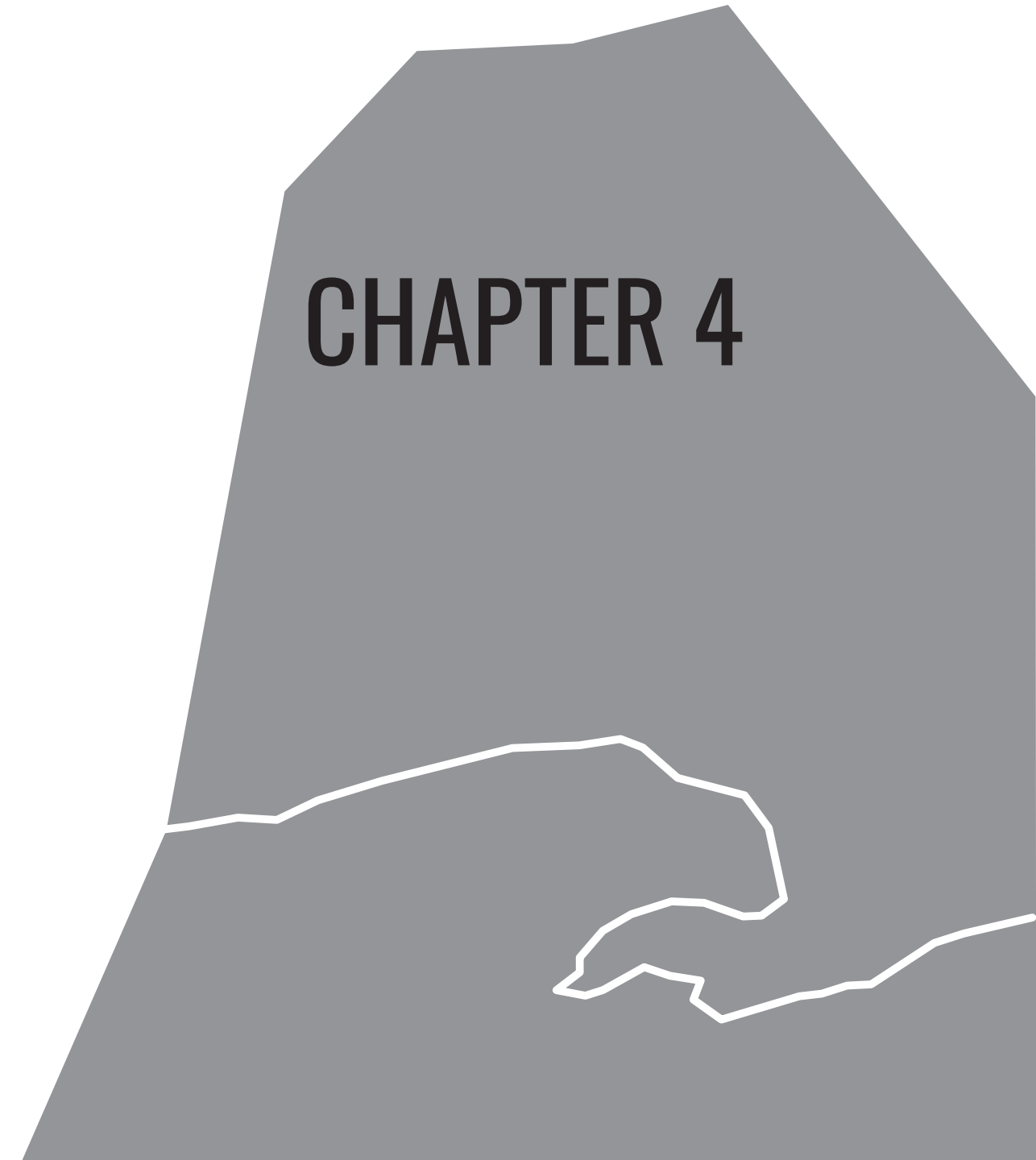
CHAPTER 4



METHOTREXATE FOR MAINTAINING REMISSION IN PEDIATRIC CROHN'S PATIENTS WITH PRIOR FAILURE OR INTOLERANCE TO THIOPURINES: A MULTICENTER COHORT STUDY

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Journal of Crohn's and Colitis, 2015, 305–311

ABSTRACT

Background: Methotrexate (MTX) is an immunomodulating drug that can be used to maintain remission in patients with Crohn's disease (CD), but data on efficacy and tolerability in children and teenagers are scarce.
We evaluated the long-term efficacy and tolerability of MTX monotherapy after thiopurine therapy in pediatric CD patients.

Methods: A multicentre cohort of pediatric MTX users who stopped thiopurines due to ineffectiveness or intolerance between 2002 and 2012 were included and followed for at least 12 months. Relapse-free use was defined as steroid and biologic-free clinical remission after the introduction of MTX, and included intentional discontinuation of successful therapy before the end of the observation period.

Results: One hundred thirteen patients with CD in remission were followed while on MTX monotherapy, of which 75 (66%) had failed on thiopurines and 38 (34%) had stopped thiopurines due to side effects. Median age at the introduction of MTX was 14 years (range 7 to 17), and 93% used the subcutaneous route. Kaplan–Meier analysis showed that 52% of the study cohort was still in steroid and biologic-free remission after 12 months of MTX monotherapy, with a difference that did not reach significance between thiopurine intolerant and thiopurine failing patients (P=0.21, log-rank test).

Conclusions: The findings of this cohort study suggest that MTX is an effective immunomodulator to maintain remission after stopping thiopurines. MTX maintenance should be considered before stepping up to anti-TNF-alpha therapy. It is probably somewhat more effective in patients who stopped thiopurines due to side effects than in those who failed on thiopurines.

INTRODUCTION

Approximately 30% of patients with Crohn's Disease (CD) present before the age of 19 years.[1] Treatment is aimed at inducing and maintaining remission of disease activity to ensure normal growth and pubertal development, and improving the quality of life of patients. European guidelines recommend the use of exclusive enteral nutrition or steroids to induce remission in children with luminal CD.[2] Thiopurines (azathioprine or mercaptopurine) or methotrexate are recommended to maintain steroid free remission.[2] Methotrexate (MTX) appears to be similarly effective in maintaining clinical remission as thiopurines,[3-9] but side effects (including nausea, vomiting and elevated liver enzymes) have deterred its widespread use. Studies focusing on long-term benefits of MTX maintenance therapy in pediatric CD are lacking, and most published studies have lumped together children who stopped thiopurines due to intolerance (not true failures) and those who failed to respond to thiopurines[3,4,7-9] Unfamiliarity with MTX make pediatric gastroenterologists to frequently omit this drug and move on to infliximab, which has a limited duration of effect to maintain remission.[10,11] Increasingly tight healthcare budgets and concerns about the lymphoproliferative risk of long-term use of thiopurines have ignited a renewed interest among adult and pediatric gastroenterologists in MTX.
We aimed to evaluate the long-term efficacy and tolerability of MTX monotherapy in a cohort of Dutch children and teenagers with CD and distinguished patients who failed on thiopurines and those who discontinued due to side effects.

MATERIALS & METHODS

Study design & setting

In this retrospective multicentre cohort study we evaluated patient data from 6 university and 4 general teaching hospitals. The participating pediatric gastroenterologists are members of the Kids with Crohn's and Colitis (KiCC) working group for Collaborative Research in the Netherlands. Together they treat about two-thirds of the total pediatric CD population in the Netherlands. Data were entered on site in an electronic case report form that was specifically designed for this research project and included patient and disease characteristics (expressed

according to the Paris classification[12]), previous therapies and disease course. We especially focused on the period of exposure to MTX, clinical efficacy (expressed as relapse-free use) and tolerability.

Participants
We identified children and teenagers (up to the age of 17) with CD who were treated with MTX after thiopurine ineffectiveness or intolerance between 2002 and 2012. For patients with several episodes of MTX exposure, we only analyzed the first episode. Those who used MTX primarily to treat a non-IBD indication (e.g. rheumatoid arthritis) and those on anti-TNF-alpha co-treatment were excluded from analysis.

Definitions & outcome measures
Primary outcome measure was relapse-free MTX use, which was defined as either steroid or biologics-free clinical remission after the introduction of MTX, and included intentional discontinuation of successful MTX therapy before the end of the observation period. Among patients who discontinued successful MTX therapy we distinguished those who did so per provider recommendation and those who self-initiated discontinuation. Whenever available, endoscopic and pathohistologic reports were used to confirm relapse. As this is an uncommon strategy to determine relapse in pediatric CD, we based this diagnosis mainly on a Pediatric Crohn's Disease Activity Index (PCDAI) score > 10 points in combination with the initiation of steroids, anti-TNF-alpha therapy or exclusive enteral nutrition.
Secondary outcome measures included the occurrence of side effects, reasons for discontinuation, and identification of risk factors for relapse under MTX monotherapy. Early failure of MTX-treatment was defined as relapse within 6 months after initiation of MTX.

Statistical analysis
Data were analyzed with SPSS for Windows, version 20 (SPSS Inc, Chicago, IL). All tests were two-sided and the level of significance used was $P < 0.05$. Time-to-event data were analyzed by Kaplan-Meier and log-rank test. Stepwise logistic regression with backward elimination was planned to determine predictors of early MTX failure. Candidate predictors with $P < 0.10$ in bivariate analysis were selected for use in the multivariate analysis. This level was chosen because of the limited number of patients in the analysis.

Table 1. Patient characteristics prior to the start of methotrexate (n=113)

Characteristics
Female
Median age at diagnosis (range in years)
IBD-related comorbidity
■ Joint inflammation
■ Eye manifestations
■ Skin manifestations
Initial remission induction therapy
■ Exclusive enteral nutrition
■ Steroids
■ Aminosalicylates
■ Azathiopurine
Initial maintenance therapy
■ Azathiopurine
■ Aminosalicylates
Thiopurine switch to mercaptopurine prior to MTX
Median number of relapses prior to MTX (range)
Disease behavior (according to Paris Classification[12])
■ B1
■ B2
■ p
■ B1, p
■ B2, p
■ B2B3,p
Growth delay (according to Paris Classification[12])

B1: Nonstricturing, nonpenetrating disease, B2: Stricturing disease, B3: penetrating disease, p: perianal disease modifier, B2B3: both penetrating and stricturing disease either at the same or different times.

Thiopurine failure (n=75)	Thiopurine intolerance (n=38)	Total (n=113)
43%	40%	42%
13 (4-17)	14 (8-18)	13 (4-18)
8%	13%	10%
3%	11%	5%
16%	8%	13%
60%	71%	64%
37%	29%	35%
1%	-	1%
1%	-	1%
87%	90%	88%
13%	10%	12%
20%	29%	23%
2 (0-4)	1 (0-4)	2 (0-4)
47%	66%	53%
16%	8%	13%
16%	8%	13%
1%	3%	2%
5%	5%	5%
1%	-	1%
20%	16%	19%

Ethical considerations

This study was not subject to "Medical Research Involving Human Subjects Act", as it involved the study collection of data generated by routine medical care. The data were collected and recorded by the investigators in such a manner that subjects could not be identified, directly or through identifiers linked to the subjects.

RESULTS

Patient characteristics

We identified 148 children and teenagers who started MTX therapy between 2002 and 2012. A total of 35 children were excluded from analysis for anti-TNF-alpha cotreatment (n=29), MTX use primarily for a non-IBD indication (n=3), or missing values (n=3). A total of 113 methotrexate users were ultimately included, of which 75 (66%) had failed on thiopurines and 38 (34%) discontinued thiopurines due to side effects. Two-thirds were initially treated with exclusive enteral nutrition to induce remission, and 88% received azathioprine as their first immunomodulator. The majority of cases had nonstricturing, nonpenetrating luminal CD (table 1).

MTX was initiated at a median age of 14 years (range 7 to 17) and after a median disease duration of 2 years (range 1 month to 11 years) (table 2). Seventy-one percent of the patients who discontinued thiopurine monotherapy because of intolerance had drug-induced acute pancreatitis. Most patients received MTX subcutaneously (93%) at initiation, with a median dosage of 15 mg/wk (range 5 to 25), which is equivalent to 11 to 15 mg/m2 (body surface area). All patients in this study cohort received folate within 24 to 48 hours after the administration of MTX.

Duration of methotrexate use

Eighteen months after introduction over 50% of our cohort was still using MTX. At 3, 6, 12 and 24 months, the proportions of patients on continuous use of MTX were 94% (95% CI: 89 to 98), 83% (95% CI: 76 to 90), 65% (95% CI: 56 to 73) and 44% (95% CI: 35 to 54) respectively. A fifth of our cohort used MTX for more than 3 years.

Among those who discontinued MTX, 45% did so because of ineffectiveness, while 47% had intolerance. The remainder stopped successful MTX therapy per provider recommendation (n=5) or on their own initiative (n=2).

Table 2. Patient characteristics at initiation of methotrexate maintenance therapy (n=113)

Reason for initiation of MTX	
■ Thiopurine ineffectiveness	66%
■ Thiopurine intolerance	34%
▫ Pancreatitis	24%
▫ Hepato/myeolotoxicity	5%
▫ Other complaints	4%
Median age at initiation of MTX (range in years)	14 (7-17)
Median disease duration at initiation of MTX (range in years)	2 (0.1-11)
MTX route of administration	
■ Subcutaneous	93%
■ Oral	7%

MTX, methotrexate

Efficacy of methotrexate

Steroid and biologics-free MTX use is shown in figure 1. Nine patients were excluded from this time-to-event analysis as they did not reach remission while using MTX. Fifty-two percent of the total study cohort (95% CI: 42 to 62%) was still in steroid and biologic-free remission after 12 months of MTX monotherapy (line not shown), with a difference that did not reach significance between thiopurine intolerant and thiopurine failing patients (P=0.21, log-rank test). In the first group the percent of relapse-free children at 6, 12 and 24 months was respectively 85% (95% CI 72 to 97%), 62% (95% CI 44 to 79%) and 38% (95% CI 20 to 56%), while in the group who previously failed on thiopurines the percent of relapse-free children was respectively 67% (95% CI 66 to 69%), 48% (95% CI 36 to 60%) and 25% (95% CI 14 to 37%) . We intended to construct a prognostic model for discontinuation of MTX-treatment. Stepwise logistic regression with backward elimination was planned, but in the bivariate model only one significant risk factor was identified. Multivariate analysis was therefore not executed. Ineffectiveness of thiopurine before intiation of MTX was a significant risk factor for subsequent early MTX failure (odds ratio 2.6 (95% CI 1.1 to 6.5), P= 0,036).

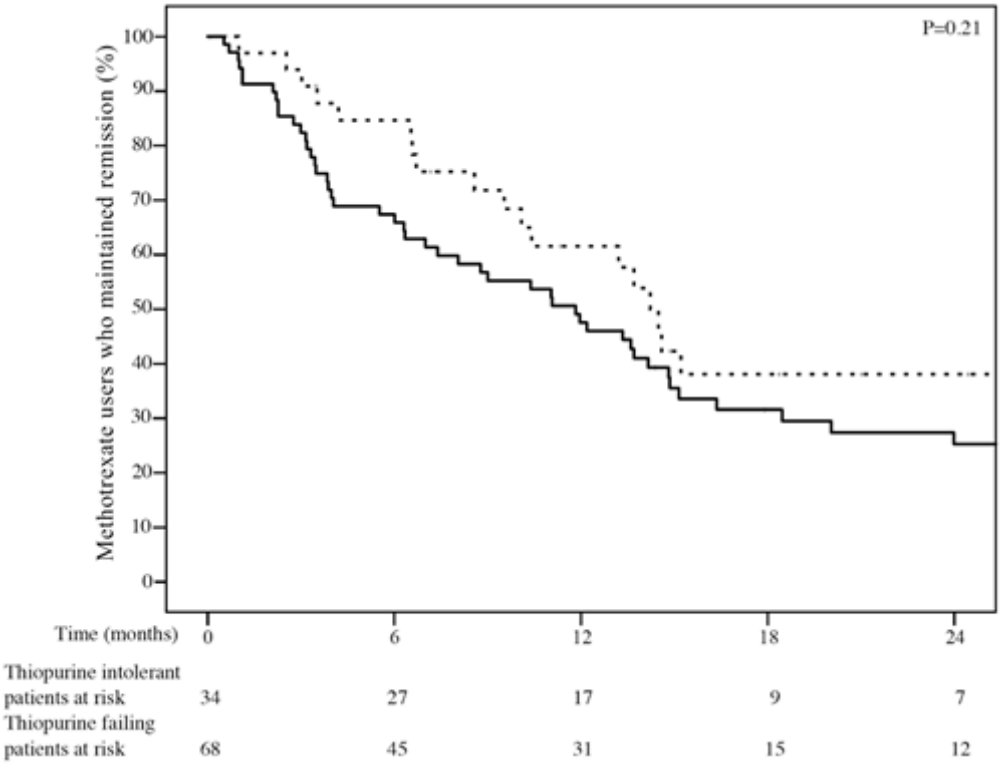

Figure 1. Kaplan-Meier plot demonstrating the percent of methotrexate users who maintained remission. Children with Crohn's disease who failed on thiopurines (solid line) are compared with those who discontinued thiopurines due to side effects (dotted line). Event is defined as date of first relapse, necessitating steroids, exclusive enteral nutrition or anti-TNF-alpha therapy; censor is defined as discontinuation of methotrexate due to side effects or end of observation period. The numbers on the lowest two lines indicate the number of patients being represented at that point in time.

Safety and prevention

Sixty-eight of 113 patients reported side effects. The commonest complaint was nausea and/or vomiting around MTX administration (figure 2). This resulted in discontinuation of MTX therapy in 21 patients. Thirty patients received ondansetron. In the majority of cases (n=18) this premedication strategy was only started after the appearance of side effects. Six of 113 patients had transient elevation of transaminases, of which one developed regenerative nodular liver hyperplasia. In two cases transaminitis resolved after dose tapering or temporary discontinuation. In the remaining four MTX was permanently discontinued.

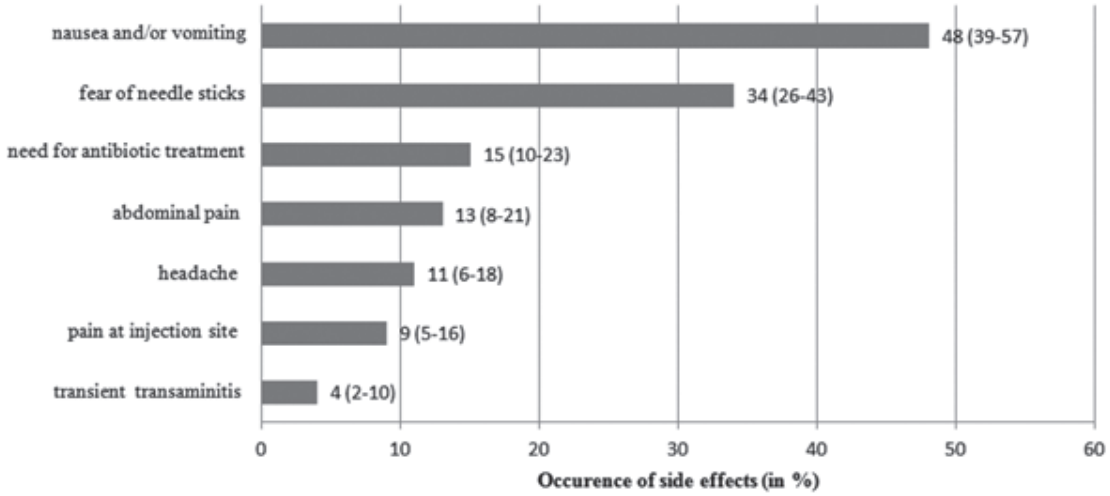

Figure 2. Percentage of patients reporting side effects (with 95% confidence intervals), n=113.

DISCUSSION

Key results

We studied the efficacy and tolerability of methotrexate monotherapy in children with CD who discontinued thiopurines. Twelve months after initiation of MTX 52% of the patients was still free from relapse. MTX efficacy in the group of patients who had thiopurine intolerance was not superior to MTX efficacy in the group of patients with thiopurine failure. Nausea and/or vomiting around MTX administration were the most common side effects prompting 19% of patients to stop MTX.

Comparison with other studies

To our knowledge this is the largest study that evaluated the efficacy of MTX after discontinuation of thiopurines and divided MTX users into those who failed on thiopurines and those who stopped due to side effects. Most papers that have been published to date (table 3) were case series describing the proportion of patients in remission at preset time points, and may have underestimated its real protective effect. In previously published studies the percentage of patients still in remission after 12 months ranged from 33 to 48%.[3-9,13,14] In order to evaluate the

Table 3. Overview of studies reporting methotrexate efficacy after thiopurine use in pediatric luminal Crohn's disease

Reference	Patients	Design	Age at start MTX (yrs)
Mack, 1998 [3]	14	Prospective and retrospective case series	15.1 ± 3.1 (mean, SD)
Uhlen, 2006 [4]	61	Retrospective case series	Age at diagnosis, 11.1 ± 2.3 (mean, SD); duration until start MTX, 3.1 ± 2.2
Turner, 2007 [5]	60	Retrospective case series	13.8 ± 2.7 (mean, SD)
Ravikumara, 2007 [9]	10	Retrospective case series	15.8 (median, range 12 to 16.9)
Weiss, 2009 [6]	25	Retrospective case series	14.5 ± 3.1 (mean, SD)
Boyle, 2010 [7]	27	Retrospective case series	13.8 ± 0.7 (mean, SD)
Sunseri, 2014 [13]	91	Retrospective cohort study	Unknown
Turner, 2014 [14]	226	Retrospective cohort study	13,8 ± 2,8 (mean, SD)

Previous immuno-modulator treatment	Primary outcome	Result
MP	PCDAI –score and steroid requirement	64% showed improvement (PCDAI-score decreased from baseline)
AZA	HBI and steroid requirement	39%, 49% and 45% complete remission at 3, 6 and 12 months respectively
AZA and MP	PCDAI-score, steroid requirement and height velocity	62% and 53% in full remission (PCDAI < 10) at 6 and 12 months respectively. 42% in remission at both 6 and 12 months
AZA, EEN and 5-ASA	Clinical symptoms and inflammatory markers	7 children showed clinical and biochemical improvement
AZA and MP	HBI and steroid requirement	64% achieved remission, 24% partial response and 48% in remission or response at 12 months
AZA and MP	Steroid/Infliximab free remission determined by PGA	48% and 33% in remission at 6 and 12 months respectively
Thiopurine, not further specified	Remission determined by PGA, without surgery, TP, biologicals or corticosteroids	35% had sustained clinical remission for 12-48 months
Thiopurines and 5-ASA	Remission determined by PCDAI or inactive perianal fistula, without treatment escalation or surgery surgery	34% had sustained steroid-free remission for 12 months

true relapse-preventing effect of MTX, patients should ideally only be included in a study cohort after they have reached remission, have stopped steroids or exclusive enteral feeding, and use MTX monotherapy (figure 3).[15] Whether this is done in previously published studies is not clearly described. We used a strict case definition for clinical remission that was based on PCDAI-score < 10 (and where applicable fecal calprotectin levels in the normal range, i.e. < 250 µg/g) without treatment escalation (i.e. adding steroids, exclusive enteral nutrition or anti-TNF-alpha).[16,17] Secondly, in contrast to previously published studies we classified patients who discontinued successful MTX use per provider recommendation or on their own initiative under relapse-free MTX use and not under treatment failure.

Methodological limitations

Relapse-free MTX use was our primary outcome, but due to the retrospective nature of this study discontinuation of the drug was not determined by protocol. Physicians with a pre-existing bias against MTX may have seen the appearance of side effects as a confirmation of the patient-unfriendly medicine and were perhaps easier in moving forward to anti-TNF therapy. Others may have put more effort in treating the side effects, e.g. with ondansetron.[18] Another possible restriction of this study related to the method of retrospective chart review, which may have affected the reliability of reporting of side effects and non-adherence. In addition the impact of MTX treatment on endoscopic disease activity (i.e. mucosal healing) was not assessed.

Implications for pediatric practice

Few pediatric gastroenterologists prescribe MTX in CD patients on a regular basis, in contrast to rheumatologists in the treatment of patients with rheumatoid arthritis.[19] Skepticism about its effectiveness, concerns about adverse events and lack of experience with the drug are the main reasons to omit MTX as a second line immunomodulator and to prescribe more expensive anti-TNF-alpha antibodies following thiopurine ineffectiveness or intolerance. In the Netherlands annual drug costs to treat a 40 kg weighing child with CD is €1381 for weekly subcutaneous injections of methotrexate and €7656 for 8-weekly intravenous infliximab infusions.[20] In this calculation we did not take into account the additional costs for intravenous infusions during hospital day admissions. The findings of this cohort study suggest

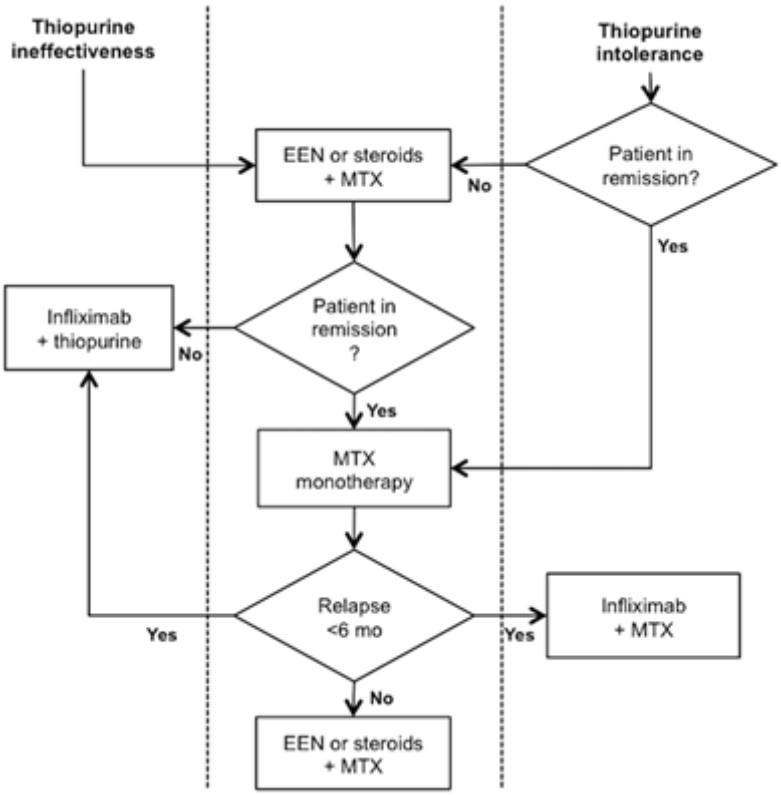

Figure 3. Position of methotrexate in step-up treatment scheme for pediatric luminal CD used in this study cohort15 EEN, Exclusive enteral nutrition; MTX, methotrexate. Relapse preventing effect of MTX is assessable once MTX montherapy is initiated

that it is worthwhile to consider MTX to maintain remission, before stepping up to anti-TNF-alpha antibodies. Over 50% of the study cohort was relapse free a year after introducing MTX and a fifth of the cohort used it satisfactorily for more than 3 years.
A recently published multi-center observational study from North-America showed that MTX is being prescribed with increasing frequency as first choice immunomodulator. Many pediatric gastroenterologists seem to become uncomfortable with thiopurines usage, particularly in conjunction with anti-TNF-alpha antibodies.[13]

Nausea and/or vomiting were the most common side effects following MTX and an important reason to stop MTX, even if the treatment was successful in maintaining remission. Many children will develop anticipatory vomiting, which is vomiting

prior to the administration of MTX. It is a learned response that is more likely to happen in children who have a history of motion sickness. Administration of ondansetron from the outset one hour prior to injection may reduce anticipatory nausea and could improve tolerance.[18] In our cohort ondansetron was only used in 30 patients and mostly after the appearance of complaints. We did not observe a statistically significant difference between preemptive and post hoc administration of ondansetron regarding MTX tolerance.

Abnormal liver biochemistry was seen in 5% of our cohort. Dose reduction or a short MTX holiday could solve the transaminitis, but in the majority of cases the patient was advised to discontinue MTX permanently. In a recently published systematic review that included 457 pediatric CD cases treated with MTX, approximately 10% (95% CI 5 to 19%) had signs of transaminitis. (21 Patients in stable remission should have their alanine aminot) ransferase monitored periodically. Several authors recommend folate supplementation in order to decrease the severity of gastrointestinal symptoms and liver toxicity.[22-24]

Whether MTX can be administered orally for maintaining remission has been largely debated in the literature. Bioavailability of oral MTX varies highly, in particular in CD patients with small-bowel disease. A recently published retrospective cohort study among children with CD treated with oral or subcutaneous MTX suggests that MTX should be commenced subcutaneously and could be switched to the oral route once complete remission is reached.[14] The majority of CD patients in our cohort (93%) were treated with subcutaneous MTX.[15] The mean weekly dose was 15 mg/m2 body surface area and was similar to the dosage used in other pediatric studies.[14]

CONCLUSION

This cohort study among pediatric CD patients who received MTX monotherapy following discontinuation of thiopurines showed that 52% was still relapse-free 12 months after initiation, decreasing to 29% after 24 months. Nausea and vomiting around administration was observed in half of the cohort, and was an important reason to discontinue MTX, despite steroids and biologics free clinical remission. Our findings suggest that it is worthwhile to consider MTX to maintain remission, especially in those who are thiopurine intolerant, before stepping up to anti-TNF-alpha antibodies. Preemptive treatment with an anti-emetic may improve MTX tolerance.

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Part II

Optimizing accuracy of fecal calprotectin measurements in disease monitoring