METHOTREXATE AFTER THIOPURINE THERAPY IN CHILDREN WITH CROHN’S DISEASE: A MULTICENTER COHORT STUDY

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Abstract

METHOTREXATE AFTER THIOPURINE THERAPY IN CHILDREN WITH CROHN’S DISEASE: A MULTICENTER COHORT STUDY

BACKGROUND:
Methotrexate (MTX) is an immunomodulating drug that can be used to maintain remission in patients with Crohn’s disease (CD). It is underused in the routine care of children with CD. Data on the efficacy and tolerability in children and teenagers are scarce. We assessed the clinical efficacy and tolerability of MTX monotherapy after thiopurine therapy in a large Dutch pediatric cohort.

METHODS:
We analyzed data from 6 university and 4 general teaching hospitals on consecutive children and teenagers who received MTX after thiopurine ineffectiveness or intolerance. We assessed patient characteristics, tolerability and benefits of the treatment. Clinical benefit was defined as ongoing use of MTX without relapse, or intentional discontinuation of successful therapy before the end of the observation period.

RESULTS:
We identified 113 consecutive children who started MTX therapy between 2002 and 2012. Median age at the start of MTX therapy was 14 years (range 7 to 17). The proportion of children with clinical benefits were 73%, 52%, and 29%, at 6, 12, and 24 months, respectively. Thirty-one children discontinued MTX because of intolerance. Nausea or vomiting around administration was the commonest adverse event in MTX-intolerant patients (48%). Failure of preceding thiopurine treatment was a predictor for CD relapse within 6 months after starting with MTX.

LIMITATIONS:
Nine patients were excluded from the Kaplan-Meier survival analysis for not being in remission at the start of the observation period. An objective appraisal of the remission-maintaining properties of MTX was not possible in these patients.

CONCLUSIONS:
Among pediatric CD patients who received MTX therapy after thiopurine, 52% still experienced clinical benefits 12 months after the start. Pre-emptive treatment with an anti-emetic to reduce adverse events was underused.
## Contents

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1. Introduction

An estimated total of 250 new pediatric inflammatory bowel disease patients are diagnosed each year in the Netherlands. The majority is diagnosed with Crohn’s disease (CD), a transmural and often granulomatous inflammation that involves the entire gastro-intestinal tract in a discontinuous manner. The disease is characterized by unpredictable bouts of increased inflammation (relapses) and periods with remission.

Treatment is aimed at inducing and maintaining remission of disease activity, thus facilitating normal growth and pubertal development, and thereby improving the quality of life of patients. Corticosteroids or exclusive enteral nutrition may be effective for induction of remission. Thiopurines (azathioprine or 6-mercaptopurine) are recommended as first choice for maintenance of steroid free remission in children.\textsuperscript{2-3} Methotrexate (MTX) appears to be similarly effective in maintaining clinical remission as the thiopurines, but there are no prospective pediatric randomized controlled trials.\textsuperscript{4-9} Due to the need for initial subcutaneous administration and more common adverse events (including nausea, vomiting and elevated liver enzymes) it is considered a second-line immunomodulator.

First time MTX was suggested as an effective treatment in inflammatory bowel disease patients was in 1989.\textsuperscript{10} This was based on its effectiveness in two other chronic inflammatory diseases, rheumatoid arthritis and psoriasis. Several clinical trials and analyses of clinical notes followed and have examined the role of MTX in CD in adults.\textsuperscript{11-17} There is scarcity of information on the use of MTX in children with CD. Many clinical questions remain, including appropriate dosing and administration of MTX after discontinuation of thiopurines, feasibility of oral administration and long term safety. Unfamiliarity with MTX in combination with its infamous adverse events make clinicians to omit this drug and immediately move on to prescribing expensive anti-TNF-alpha antibodies. Facing increasingly tight healthcare budgets, it may be appropriate to reconsider the unpopular position of MTX.

We aimed to evaluate the efficacy and safety of MTX in a cohort of Dutch children and teenagers with CD. Primary outcome measure was relapse-free survival with MTX. Secondary outcome measures included the occurrence of adverse events, reasons for discontinuation, and identification of risk factors for relapse during MTX maintenance treatment.
2. Methods

2.1 Study design & setting

In a multicenter cohort study we evaluated routinely collected 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. 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\textsuperscript{18}), previous therapies and disease course. We especially focused on the period of exposure to MTX, clinical efficacy and tolerability.

2.2 Participants & potential bias

We identified all consecutive children and teenagers (up to the age of 17) with CD who were treated with MTX on second instance 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.

2.3 Definitions & outcome measures

Primary outcome measure was sustained clinical benefit of MTX. Clinical benefit was defined as ongoing use of MTX without relapse, or intentional discontinuation of successful therapy before the end of the observation period. In the absence of a gold standard for relapse, we used a clinical case definition incorporating fecal calprotectin, C-reactive protein, erythrocyte sedimentation rate and Pediatric Crohn’s Disease Activity Index.\textsuperscript{18-20} Through this case definition the level of reliability of the diagnostic evidence was established: confirmed vs. probable vs. possible relapse (Box 1).

Box 1. Case definition relapse
(In absence of endoscopy)

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fecal calprotectine &gt; 250ug/g</td>
</tr>
<tr>
<td>- CRP &gt; 10mg/L</td>
</tr>
<tr>
<td>- ESR &gt; 20 mm/u</td>
</tr>
<tr>
<td>- PCDAI-score &gt; 10 points</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criterium</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Thrombocytes &gt; 450 x 10\textsuperscript{9}/L</td>
</tr>
</tbody>
</table>

**Confirmed relapse:** All major criteria present  
**Probable relapse:** Two or more major criteria present  
**Possible relapse:** One major and one minor criterium present
Secondary outcome measures included the occurrence of adverse events, reasons for discontinuation, and identification of risk factors for relapse under MTX immunomodulation. Failure of MTX-treatment was defined as relapse within 6 months after initiation of MTX.

2.4 Statistical analysis & study size

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 $P < 0.05$. Kaplan-Meier survival analysis was used to estimate the probability of relapse-free survival with MTX and also to determine treatment duration of MTX. Stepwise logistic regression with backward elimination was planned to determine predictors for 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.
3. Results

3.1 Patient characteristics

We identified 148 children and teenagers who started MTX therapy between 2002 and 2012. A total of 35 were excluded from analysis for anti-TNF-alpha cotreatment (n=29), MTX use primarily for a non-IBD indication (n=3), or incomplete follow-up (n=3). A total of 113 patients were eligible for inclusion, of which 42% were female (table 1). The median age at diagnosis was 13 (range 4 to 18) years. Two thirds were initially treated with exclusive enteral nutrition, and azathioprine was the immunomodulator of choice (88%). The majority of cases had nonstricturing, nonpenetrating disease. The distribution of the site of initial inflammation in our cohort was not significantly different from a general pediatric CD population (figure 1).

Table 1. Patient characteristics prior to MTX

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>42 (33-51)</td>
</tr>
<tr>
<td>Median age at diagnosis (range)</td>
<td>13 (4-18)</td>
</tr>
<tr>
<td>IBD-related co morbidity:</td>
<td></td>
</tr>
<tr>
<td>- Joint inflammation</td>
<td>10 (6-17)</td>
</tr>
<tr>
<td>- Eye manifestations</td>
<td>5 (3-11)</td>
</tr>
<tr>
<td>- Skin manifestations</td>
<td>13 (8-21)</td>
</tr>
<tr>
<td>- Bile and liver disorders</td>
<td>0</td>
</tr>
<tr>
<td>Initial remission induction therapy</td>
<td></td>
</tr>
<tr>
<td>- Exclusive enteral nutrition</td>
<td>64 (54-74)</td>
</tr>
<tr>
<td>- Steroids</td>
<td>35 (25-44)</td>
</tr>
<tr>
<td>- Aminosalicylates</td>
<td>1 (0-11)</td>
</tr>
<tr>
<td>- Azathiopurine</td>
<td>1 (0-11)</td>
</tr>
<tr>
<td>Initial immunomodulator therapy*</td>
<td></td>
</tr>
<tr>
<td>- Azathiopurine</td>
<td>88 (82-94)</td>
</tr>
<tr>
<td>Thiopurine switch prior to MTX</td>
<td>23 (16-32)</td>
</tr>
<tr>
<td>Median number of relapses prior to MTX (range)</td>
<td>2 (0-4)</td>
</tr>
<tr>
<td>Disease behavior (according to Paris Classification)</td>
<td></td>
</tr>
<tr>
<td>- B1</td>
<td>53 (29-77)</td>
</tr>
<tr>
<td>- B2</td>
<td>13 (0-49)</td>
</tr>
<tr>
<td>- p</td>
<td>13 (0-49)</td>
</tr>
<tr>
<td>- B1, p</td>
<td>2 (0-26)</td>
</tr>
<tr>
<td>- B2, p</td>
<td>5 (0-29)</td>
</tr>
<tr>
<td>- B2B3, p</td>
<td>1 (0-25)</td>
</tr>
<tr>
<td>Growth delay (according to Paris Classification)18)</td>
<td>19 (10-27)</td>
</tr>
</tbody>
</table>

Data are presented as proportions with 95% confidence intervals, unless stated otherwise

* The remainder 12% did not receive any immunomodulator, but instead used aminosalicylates.

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.
3.2 Methotrexate treatment

MTX was initiated at a median age of 14 years (range 7 to 18) and after a median disease duration of 2 years (range 0 to 11) (table 2). Most common reason to start MTX was failure of thiopurines (n=73). Out of thirty-eight patients who discontinued first line treatment because of intolerance, twenty-seven stopped because of thiopurine associated pancreatitis. Most patients received MTX subcutaneously (93%) at initiation, with a median dosage of 15mg/wk (range 5 to 25).

Eighteen months after introduction over 50% of our cohort was still using MTX. At 3, 6, 12 and 24 months, the proportions of patients with ongoing 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). A fifth of our cohort used MTX for more than 3 years.

Main reason to discontinue treatment was ineffectiveness of MTX (51%) (figure 2). Discontinuation because of MTX intolerance occurred in 40% of the study population. Eight patients intentionally stopped MTX because of prolonged sustained remission (> 3 years).
Table 2. Patient characteristics at initiation of MTX

<table>
<thead>
<tr>
<th>Reason for initiation of MTX</th>
<th>n=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of thiopurine</td>
<td>65 (55-73)</td>
</tr>
<tr>
<td>Thiopurine intolerance</td>
<td>33 (26-43)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>24 (17-33)</td>
</tr>
<tr>
<td>Hepato/myelotoxiciteit</td>
<td>5 (3-11)</td>
</tr>
<tr>
<td>Other complaints</td>
<td>4 (2-10)</td>
</tr>
<tr>
<td>Rheumatologist advised to switch to MTX for better disease modifying properties</td>
<td>2 (1-6)</td>
</tr>
</tbody>
</table>

Median age at initiation of MTX (range)                            | 14 (7-18) |
Median disease duration at initiation of MTX (range)               | 2 (0-11) |
MTX route of administration                                        |         |
Subcutaneous                                                      | 93 (87-96) |
Oral                                                              | 7 (4-13) |

Data are presented as proportions with 95% Confidence intervals, unless stated otherwise

Figure 2. Reasons for discontinuation of MTX in proportions (n=88)
3.3 Efficacy of methotrexate

Relapse-free survival during MTX use is shown in figure 3. The proportion of children with clinical benefit at 6, 12 and 24 months was respectively 73% (95% CI: 65 to 82%), 52% (95% CI: 42 to 62%) and 29% (95% CI: 20 to 39%). Four patients intentionally discontinued successful therapy before the end of the observation period. At the end of the observation period 11 patients still experienced clinical benefits on MTX monotherapy. Nineteen patients were forced to stop successful treatment because of intolerance. Patient and disease characteristics of the nine excluded patients are shown in table 3.

![Relapse-free survival after initiation of MTX](image)

**Figure 3.** Relapse-free survival after initiation of MTX

Event was defined as date of first relapse, necessitating steroids or EEN; censor was defined as discontinuation due to side-effects or intolerability.
Table 3. Summary of excluded patients from the Survival analysis in figure 3

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at initiation of MTX (in years)</th>
<th>Disease location &amp; behavior (according to Paris Classification)</th>
<th>Duration of MTX-treatment in months</th>
<th>Treatment after discontinuation of MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>L2L4a,B2</td>
<td>4</td>
<td>Infliximab monotherapy</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>L3L4a, B2</td>
<td>3</td>
<td>Infliximab monotherapy</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>L3L4a, B1</td>
<td>13</td>
<td>Lanvis + Corticosteroids</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>L1,p</td>
<td>3</td>
<td>Humira monotherapy</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>L3,B1</td>
<td>5</td>
<td>Infliximab monotherapy</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>-</td>
<td>4</td>
<td>Infliximab monotherapy</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>L3L4ab</td>
<td>5</td>
<td>Not applicable</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>L3,p</td>
<td>5</td>
<td>Humira monotherapy</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>L3,p</td>
<td>2</td>
<td>Infliximab monotherapy</td>
</tr>
</tbody>
</table>

Nine patients were excluded from Kaplan-Meier analysis as they did not reach remission while using MTX. B1: Nonstricturing, nonpenetrating disease, B2: Stricturing disease, p: perianal disease modifier
3.4 Predictors of MTX-failure

We planned to construct a prognostic model for failure of MTX-treatment. Failure was defined as relapse within 6 months after initiation of MTX. Stepwise logistic regression with backward elimination was planned, but in the bivariate model only one significant risk factor was identified (table 4). Multivariate analysis was therefore not executed. ‘Failure of thiopurine before intiation of MTX was a significant risk factor for subsequent MTX failure (odds ratio 2.6 (95% CI 1.1 to 6.5), P= 0.036).

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Bivariate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration at the initiation of MTX treatment in years</td>
<td>0.203</td>
<td>0.081</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>Amount of relapses after diagnostic endoscopy until initiation of MTX</td>
<td>0.308</td>
<td>0.142</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>Failure of thiopurine before initiation of MTX</td>
<td>0.969</td>
<td>0.036</td>
<td>2.6 (1.1-6.5)</td>
</tr>
<tr>
<td>Route of administration*</td>
<td>0.780</td>
<td>0.290</td>
<td>2.2 (0.5-9.3)</td>
</tr>
<tr>
<td>Responsibility for medication*</td>
<td>0.693</td>
<td>0.135</td>
<td>2.0 (0.8-5.0)</td>
</tr>
</tbody>
</table>

*binary variables are coded 0 for no or 1 for yes
All odds ratio’s are presented with 95% Confidence intervals
3.5 Safety and prevention

Sixty-eight of 113 patients reported adverse events. The commonest complaint was nausea and/or vomiting around MTX administration (figure 4). This resulted in discontinuation of MTX therapy in 21 patients.

In the entire cohort, thirty patients received ondansetron. In the majority of cases (n=18) this premedication strategy was only started after the appearance of adverse events. Of the 54 patients with complaints of nausea and/or vomiting, nine patients received ondansetron prior to subcutaneous MTX administration.

**Figure 4.** Proportions of adverse events reported in the entire cohort (n=113) (with 95% confidence intervals)
4. Discussion

4.1 Key results

We studied the efficacy and safety of immunomodulator therapy with methotrexate in children with CD who discontinued thiopurines. Twelve months after initiation of MTX 52% of them were still free from relapse. Patients who failed to maintain remission on thiopurines had higher risk to fail on MTX in contrast to those who switched because of thiopurine intolerance. Nausea and/or vomiting around MTX administration were the commonest side effects prompting 19% of patients to stop MTX.

4.2 Comparison with other studies

To our knowledge this is the largest pediatric study that evaluated the efficacy of MTX to maintain remission in CD. Most papers that have been published until now (table 5) were case series describing the proportion of patients in remission at preset time points, and may have underestimated its real protective effect. In earlier published studies the percentage of patients still in remission after 12 months ranged from 33 to 48%.\textsuperscript{4-8} Patients switching to MTX for ineffectiveness of thiopurines should first reach remission on steroids or exclusive enteral feeding, before the relapse-preventing effect of MTX can be assessed (figure 5). We used a strict case definition based on objective parameters (box 1) to ensure that the disease activity diminished. Secondly, the patients who intentionally stopped taking MTX without having signs of disease activity were classified under clinical benefit and not under treatment failure, despite the appearance of adverse events.
<table>
<thead>
<tr>
<th>First author &amp; publication year</th>
<th>Patients</th>
<th>Design</th>
<th>Age at start MTX (yrs)</th>
<th>Previous immunomodulator treatment</th>
<th>Primary outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mack, 1998⁴</td>
<td>14</td>
<td>Prospective and Retrospective case series</td>
<td>15.1 ± 3.1 (mean, SD)</td>
<td>6-MP</td>
<td>PCDAI-score and steroid requirement</td>
<td>64% showed improvement (PCDAI-score decreased from baseline)</td>
</tr>
<tr>
<td>Uhlen, 2006⁵</td>
<td>61</td>
<td>Retrospective case series</td>
<td>Age at diagnosis, 11.1 ± 2.3 (mean, SD); duration until start MTX, 3.1 ± 2.2</td>
<td>AZA</td>
<td>HBI and steroid requirement</td>
<td>39%, 49% and 45% complete remission at 3, 6 and 12 months respectively</td>
</tr>
<tr>
<td>Turner, 2007⁶</td>
<td>60</td>
<td>Retrospective case series</td>
<td>13.8 ± 2.7 (mean, SD)</td>
<td>AZA &amp; 6-MP</td>
<td>PCDAI-score, steroid requirement and height velocity</td>
<td>62% and 53% in full remission (PCDAI &lt; 10) at 6 and 12 months respectively, 42% in remission at both 6 and 12 months</td>
</tr>
<tr>
<td>Ravikumara, 2007²⁸</td>
<td>10</td>
<td>Retrospective case series</td>
<td>15.8 (median, range 12 to 16,9)</td>
<td>AZA, EEN and 5-ASA</td>
<td>Clinical symptoms and inflammatory markers</td>
<td>7 children showed clinical and biochemical improvement</td>
</tr>
<tr>
<td>Weiss, 2009⁷</td>
<td>25</td>
<td>Retrospective case series</td>
<td>14.5 ± 3.1 (mean, SD)</td>
<td>AZA and 6-MP</td>
<td>HBI and steroid requirement</td>
<td>64% achieved remission, 24% partial response and 48% in remission or response at 12 months</td>
</tr>
<tr>
<td>Boyle, 2010⁸</td>
<td>27</td>
<td>Retrospective case series</td>
<td>13.8 ± 0.7 (mean, SD)</td>
<td>AZA and 6-MP</td>
<td>Steroid/Infliximab free remission determined by PGA</td>
<td>48% and 33% in remission at 6 and 12 months respectively</td>
</tr>
</tbody>
</table>

6-MP, 6-Mercaptopurine; AZA, Azathiopurine; EEN, Exclusive enteral nutrition; PCDAI, Pediatric Crohn’s Disease Activity Index; HBI, Harvey-Bradshaw Index; PGA, Physicians Global Assessment
Figure 5. Position of MTX in management of pediatric CD
EEN: Exclusive enteral nutrition, MTX: methotrexate
Relapse preventing effect of MTX assessable from first diamond downwards
4.3 Methodological limitations

Clinical efficacy of MTX was our primary outcome, but due to the retrospective nature of this study the discontinuation of this drug was not determined by protocol. Physicians with a pre-existing bias against MTX may have seen the appearance of adverse events 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 adverse events, e.g. with ondansetron. Another possible restriction of this study related to the method of retrospective chart review, which may have affected the reliability of reporting of adverse reactions.

4.4 Implications for pediatric practice

Few physicians prescribe MTX in their CD patients, as opposed to children with rheumatoid arthritis. 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 expensive anti-TNF-alpha antibodies. Our findings indicate that it may be appropriate to consider using MTX in a subset of patients who discontinued thiopurines. Over 50% of our cohort was relapse free a year after introducing MTX and a fifth of the cohort used it satisfactorily for more than 3 years. We found that children who experienced thiopurine intolerance were more likely to benefit from MTX than those with thiopurine ineffectiveness.

Nausea and/or vomiting were the most common adverse events 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. 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 transaminisits, 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 hepatotoxicity. Patients in stable remission should have their ALAT monitored periodically. Several authors recommended folate supplementation in order to decrease the severity of gastrointestinal symptoms and liver toxicity. All patients in our cohort did receive folate.

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. The majority of children in our cohort (93%) were treated with subcutaneous MTX, as suggested in national guidelines. The mean weekly dose was 15 mg/m² body surface area.

4.5 Conclusion

This large cohort study among pediatric CD patients who received MTX maintenance therapy after discontinuation of thiopurines showed that approximately 50% still experienced clinical benefits 12 months after the start, decreasing to one fifth after 3 years. Nausea and vomiting around administration were seen in half of the cohort, and was an important reason to
discontinue MTX, despite successful treatment. Preemptive treatment with an anti-emetic to reduce adverse effects was underused.

4.6 Acknowledgement

We thank the members of the Kids with Crohn’s and Colitis (KiCC) working group for collaborative research for facilitating this study: Dr. A. Kindermann (Academic Medical Center, Amsterdam), Dr. G.M. Damen (UMC St Radboud Hospital, Nijmegen), Dr. L. de Ridder and Dr. H. Escher (Erasmus Medical Center/Sophia Children’s Hospital, Rotterdam), Dr. L. Mearin (LUMC, Leiden), Dr. T. de Meij (VU University Medical Center, Amsterdam), Dr. D. Hendriks and Dr. A. van den Berg (Juliana Children’s Hospital, Den Haag), Dr. E. George (Medical Centre Alkmaar, Alkmaar), Dr. T. Hummel (Medical Spectrum Twente, Enschede) en Dr. O. Norbruis (Isala Clinics, Zwolle).
6. Literature


7. Dutch abstract/Samenvatting

METHOTREXAAT NA THIOPURINE THERAPIE IN KINDEREN MET DE ZIEKTE VAN CROHN: EEN MULTICENTER COHORT STUDIE

ACHTERGROND:
Methotrexaat (MTX) is een immunomodulerend medicijn dat gebruikt kan worden als onderhoudsbehandeling bij patiënten met de ziekte van Crohn. MTX wordt niet goed benut als behandellooptie bij kinderen met de ziekte van Crohn. Gegevens over de effectiviteit en tolerantie bij kinderen en tieners is schaars. Met dit onderzoek hebben we de klinische effectiviteit en tolerantie van MTX monotherapie na thiopurine therapie bepaald in een groot cohort van kinderen in Nederland.

METHODE:
Wij zochten in de patiëntenregisters van 6 universiteit- en 4 algemeen ziekenhuizen naar informatie over kinderen en tieners die MTX kregen na het falen van- of intolerantie voor een thiopurine. We hebben patiënt karakteristieken, tolerantie en ziekteverlies door de behandeling bepaald. Ziekteverlies werd gedefinieerd als continu gebruik van MTX zonder het ervaren van een exacerbatie, of het intentioneel staken van een succesvolle behandeling voor het einde van de studie.

RESULTATEN:
Wij hebben 113 kinderen kunnen identificerden die tussen 2002 en 2012 met MTX zijn gestart. De mediaan voor leeftijd waarop MTX werd gestart was 14 jaar (range 7 tot 17). De proportie kinderen met klinische ziekteverlies was 73%, 52% en 29% na respectievelijk 6, 12 en 24 maanden. Eenendertig kinderen moesten MTX staken vanwege intolerantie. Misselijkheid en/of overgeven rondom de toediening was de meest voorkomende bijwerking (48%). Falen van een eerdere behandeling met een thiopurine was een voorspeller voor een exacerbatie van de ziekte binnen 6 maanden na het starten van MTX.

BEPERKINGEN:
9 patiënten werden niet in de Kaplan-Meier survival analyse geïncludeerd, omdat zij geen remissie hadden bereikt onder MTX. De effectiviteit van de onderhoudsbehandeling in deze patiënten kon hierdoor niet objectief worden beoordeeld.

CONCLUSIES:
Na 12 maanden gebruik, had 52% van de kinderen met de ziekte van Crohn, die MTX therapie kregen na behandeling met een thiopurine, nog steeds profijt van de behandeling. Preventieve behandeling met ondansetron om bijwerkingen te verminderen werd in deze studie onderbenut.
8. Appendix

Case Report Form

Deel 1: Patiëntkarakteristieken

Algemene patiëntinformatie

1. Ziekenhuis en patiëntnummer
   -----------------------------
2. Naam (Initialen (1e letter van alle voornamen en achterneem hoofdletter, tussevoegsel
   1e letter met kleine letter)
   -----------------------------
3. Geslacht
   1. man
   2. vrouw
4. Geboortedatum
   __-__-__
5. Gezinssituatie
   1. intact gezin
   2. eenouder gezin
6. Wie is er verantwoordelijk voor de medicatietoediening?
   1. ouder(s)
   2. kind
7. Eerstegraads familieleden met de ziekte van Crohn?
   1. ja
   2. nee
8. Beheersen de ouder(s) de Nederlandse taal?
   1. ja
   2. nee
   3. onbekend

Diagnose & behandelgeschiedenis

9. Datum diagnostische endoscopie
   __-__-__
10. Ziekte karkateristieken volgens de Paris Classification
    1. Locatie: informatie coloscopie
       o geen afwijkingen
       o L1: distal 1/3 ileum +/- limited cecal disease
       o L2: colonic
       o L3: ileocolonic
    2. Locatie: informatie OGD-scopie, MRI-enteroklyse of videocapsule
       o geen afwijkingen
       o L4a: upper disease proximal to ligament of Trietz
o L4b: upper disease distal to ligament of Trietz and proximal to distal 1/3 ileum

3. Disease behavior (combinatie mogelijk)
   o B1: non stricturerend non penetrerend
   o B2: stricturerend
   o B3: penetrerend
   o p: perianal disease modifier

4. Definitie groeiachterstand volgens Paris Classification
   o G0: geen bewijs van groei achterstand
   o G1: groei achterstand

11. IBD-gerelateerde co-morbiditeit (combinaties mogelijk)
   o nee
   o gewrichtsaandoeningen (incl. JIA)
   o lever- en galwegmanifestaties
   o oogafwijkingen (iridocyclitis, uveitis)
   o huidafwijkingen

12. Overige diagnoses?
   o ja
   o nee

1. Indien 'ja' bij vorige vraag, specificeer:

13. Primaire inductiebehandeling?
   o enterale voeding
   o steroiden
   o infliximab
   o aminosalicylaten
   o azathiopurine
   o 6-mercaptopurine

14. Primaire onderhoudsbehandeling?
   o azathiopurine
   o 6-mercaptopurine
   o infliximab
   o overig

1. Indien 'overig' bij vorige vraag, specificeer:

15. Eventuele switch van onderhoudsmedicatie?
   o ja
   o nee

16. Datum van switch
    _ _ _ _ _ _ _ _

17. Indien geswitcht, naar welk onderhoudsmedicament?
   o azathiopurine
   o 6-mercaptopurine
   o infliximab
   o overig

1. Indien 'overig' bij voorgaande vraag, specificeer:

18. Indien er geswitcht is, wat was de reden?
19. Totaal aantal relapses na diagnostische scopie en voor introductie MTX:
20. Datum laatste relapse voor introductie van MTX:

21. Start datum MTX

22. Reden voor introductie MTX?
   - falen thiopurine (falen is > 2 keer per jaar een relapse)
   - hepatotoxictiteit
   - myelotoxictiteit
   - falen monotherapie anti-TNFα
   - falen combinatietherapie anti-TNFα en thiopurine
   - voorkeur voor MTX vanwege disease modification (Reumatologie)
   - thiopurine geassocieerde pancreatitis

23. Lichaamslengte t.t.v. start MTX:
24. Gewicht t.t.v. start MTX:
25. Schoolsituatie kind t.t.v. start MTX:
   - basisschool
   - VMBO
   - HAVO
   - VWO
   - MBO
   - HBO
   - WO
   - schoolverlater

26. T.t.v. MTX introductie in leerjaar:
27. Ondersteuning voor relapse t.t.v. (of <1 mnd voor) introductie van MTX
   - ESR > 20mm/u
   - CRP > 10mg/L
   - Trombocyten > 450 x 10^9
   - Hemoglobine < -2SD (zie van Vijver, ADC 2012)
   - MCV < 77fl
   - Ferritine < 30ug/l
   - Transferrine ijzerverzadiging < 15%
   - PCDAI-score > 10 punten
   - Fecaal calprotectine > 250ug/g

28. Start dosis MTX
29. Toedieningsvorm MTX
   - subcutaan
   - intramusculair
30. Wordt er bij parenterale toediening gebruik gemaakt van een lokaal anestheticum?
   o ja
   o nee
31. Indien parenterale toedieing, wie geeft de injecties?
   o zelf
   o ouder(s)
   o verpleegkundige/thuiszorg
   o huisarts
   1. Is er een training gegeven voor het geven van de injecties?
      o ja
      o nee
   2. Indien 'ja' voorgaande vraag, specificeer:
32. Foliumzuur suppletie?
33. Ondansetron gebruik?
   1. vanaf start MTX, voor onstaan misselijkheidsklachten
      o ja
      o nee
   2. Na ontsaan misselijkheidsklachten
      o ja
      o nee

Huidige behandeling

34. Gestopt met de behandeling MTX?
   o ja
   o nee
35. Indien gestopt, stopdatum:
   _ _ _ _ _ _ _ _ _
36. Indien gestopt, stopreden:
   o klinisch ineffectief
   o intolerantie
   o wens van de patiënt
   o langdurige remissie
   o overig
   1. Specificeer voorgaande vraag:
37. Vervangende behandeling voor MTX?
   o infliximab monotherapy
   o humira monotherapy
   o infliximab met thiopurine
   o humira met thiopurine
   o geen
38. Indien MTX gebruik gecontinueerd, huidige dosis?
39. Indien MTX gebruik gecontinueerd, huidige toedieningsvorm?
   o subcutaan
   o intramusculair
   o oraal
40. Indien toedieningsvorm geswicht t.o.v. start met MTX, wat was de reden?
41. Welke co-medicatie bestaat er naast MTX gebruik?
   - voedingstherapie
   - aminosalicylaten
   - corticosteroïden lokaal
   - corticosteroïden systemisch
   - infliximab
   - adalimumab
   - ijzertherapie i.v.

42. Aantal relapses tijdens de behandeling met MTX?

43. Datum 1e relapse onder MTX?
   

Gerapporteerde bijwerkingen van MTX

44. Buikpijn?
   - ja
   - nee

45. Misselijkheid voor inname?
   - ja
   - nee

46. Misselijkheid na inname?
   - ja
   - nee

47. Braken voor inname?
   - ja
   - nee

48. Braken na inname?
   - ja
   - nee

49. Hoofdpijn?
   - ja
   - nee

50. Antibiotica gebruikt?
   - ja
   - nee

1. Indien 'ja' bij vorige vraag, specificeer:

51. Blauwe plekken?
   - ja
   - nee

52. Benauwdheid?
   - ja
   - nee

53. Indien parenterale toediening; lokale problemen rond injectiegebied?
   - ja
   - nee
54. (prik)angst?
   ○ ja
   ○ nee
55. Andere bijwerkingen ervaren?
56. Zijn er problemen in de therapietrouw gesignaleerd?
   ○ ja
   ○ nee
57. Zijn er gaandeweg bijwerkingen ontstaan en wat was de remedie?
58. Hoe vaak traden de bijwerkingen op?
   ○ eenmalig
   ○ meerdere keren
   ○ elke keer dat het medicijn werd toegediend