Concise report

Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach

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Abstract

Objective. To summarize evidence regarding the effectiveness of MTX in the treatment of childhood autoimmune chronic uveitis (ACU).

Methods. A systematic search of articles between January 1990 and June 2011 was conducted using EMBASE, Ovid MEDLINE, Evidence-Based Medicine Reviews—ACP Journal Club, the Cochrane Library and EBM Reviews. Studies investigating the efficacy of MTX as a single immunosuppressant medication in the treatment of ACU refractory to therapy with topical treatment and/or systemic treatment in children (≤ 16 years) were eligible for inclusion. The primary outcome measure was the improvement of intraocular inflammation, expressed as Tyndall, as defined by the Standardization of Uveitis Nomenclature working group criteria. The effect measure for each study was the proportion of people classified as responders. We determined a combined estimate of the proportion of children in the eligible studies responding to MTX.

Results. The initial search identified 246 articles of which 52 were potentially eligible. Nine eligible articles, all retrospective chart reviews, remained in the analysis. The number of children in studies ranged from 3 to 25, and the dose of MTX varied from 7.5 to 30 mg/m². Altogether, 95 of 135 children responded to MTX. The pooled analysis suggested that MTX has a favourable effect in the improvement of intraocular inflammation: the proportion of responding subjects was 0.73 (95% CI 0.66, 0.81).

Conclusion. Although randomized controlled trials are needed, the available evidence supports the use of MTX in the treatment of childhood ACU: approximately three-quarters of patients on MTX can expect improvement in intraocular inflammation.

Key words: methotrexate, autoimmune chronic uveitis, childhood, refractory uveitis.

Introduction

Non-infectious uveitis in childhood, with an incidence and prevalence estimated at 5 and 30 per 100 000, respectively, is a serious disease, with the potential for significant long-term complications and eventually blindness.

Although frequently associated with an underlying systemic disease, e.g. JIA, Behcet’s disease, sarcoidosis or tubulointerstitial nephritis, a significant number of cases are idiopathic. In case of refractory uveitis, early and aggressive immune-modulatory treatment, even in children, seems a reasonable approach to control inflammation, to achieve a CS-sparing effect and to decrease the risk of sight-threatening ocular damage [1]. However, there is much less experience and fewer cumulative data in treating children with uveitis or other inflammatory ocular diseases [2], and a lack of randomized controlled trials (RCTs) means that treatment with immunosuppressive drugs is supported only at evidence level III: expert opinion, clinical experience or descriptive studies [3]. MTX, a folate analogue inhibiting the enzyme
dihydrofolate reductase, is the most frequently used
immunosuppressive in the paediatric uveitis population, but
the lack of evidence from RCTs limits our understanding of
effectiveness, the optimal time to start therapy and op-
timal duration [2, 3]. Due to its common use as
steroid-sparing treatment in children, the purpose of this
review is to summarize the best available evidence to date
regarding the effectiveness of MTX in childhood autoim-
mune chronic uveitis (ACU).

Methods

Eligibility criteria

The following criteria were used to select eligible studies:
(i) patients had vision-threatening non-infectious autoim-
mune uveitis; (ii) autoimmune uveitis was refractory to
therapy with topical and/or systemic treatment, thus
showing a chronic disease course with regard to steroid
therapy according to the Standardization of Uveitis
Nomenclature (SUN) criteria, that is persistent
uveitis characterized by relapse within 3 months after dis-
continuation of therapy; (iii) patients had disease onset at
or before 16 years of age; (iv) patients received MTX as
single immunosuppressant medication for the treatment
of uveitis; (v) outcome measures to assess the effective-
ness of MTX were collected according to the SUN criteria
[4]. Intraocular inflammation was considered active or un-
controlled if the inflammatory activity was grade $\geq 1+$ at
any examination. Uveitis was defined as improved, and
MTX as successful, when its activity decreased by two
steps in the level of inflammation (anterior chamber cells
and/or vitreous haze) or decreased to grade 0 [4]. For
studies not completely adherent to the SUN criteria and
those performed before 2005, where possible, we retro-
spectively applied the SUN activity terminology with
regard to reported activity grading and only an activity
grade of 0 was considered as improved; (vi) studies
were published in English. Exclusion criteria were as fol-
lows: (i) the concomitant use of other immunosuppressant
agents in addition to MTX; (ii) starting time of MTX admin-
istration after 16 years of age; and (iii) lack of applicability/
adherence to the SUN working group criteria definition of
improvement in uveitis activity.

Outcome measures

The main outcome measure used to assess the effect of
MTX was the improvement of intraocular inflammation as
Tyndall (anterior chamber cells), according to the defin-
tion of improvement of the SUN working group criteria
[4]. As secondary outcomes, tapering and/or stopping
systemic steroid administration, improvement in visual
acuity post MTX treatment according to the SUN working
group criteria, discontinuation of MTX, time to remission
(the duration of MTX treatment needed to achieve
remission-inactive disease), time on remission on therapy
(the duration of on-going/persistent remission, while MTX
treatment continued) and time on remission off therapy
(the period with on-going/persistent remission after
discontinuing MTX treatment), and safety of administered
drug were considered.

Information sources

Publications were retrieved using a computerized search
of the following databases: EMBASE, Ovid MEDLINE,
Evidence-Based Medicine (EBM) Reviews—ACP Journal
Club, EBM Reviews—Cochrane Central Register of
Controlled Trials, EBM Reviews—Cochrane Database of
Systematic Reviews and EBM Reviews—Database of
Abstracts of Reviews of effects. Publications between
January 1990 and June 2011 were included.

Search strategy

Databases were searched with the key words chronic
uveitis or chronic iridocyclitis or recurrent uveitis or refrac-	ory uveitis or non-infectious uveitis or autoimmune uveitis
or inflammation$ eye and were crossed with Metotrexate or Methotrexate or MTX. Of note, we
did not include children, age or age limits in the search
as MeSH terms because we may have been able to ex-
trap, if possible, a subcohort of children from studies
including both children and adults. No limitation with
regard to the type of the study was entered. This strategy
excluded records related to infectious and/or supplicative
uveitis.

Study selection

Two reviewers (G.S., P.P.) independently screened the
retrieved titles and abstracts and excluded duplicates and
those obviously irrelevant. If the information in the
abstracts was insufficient to make a decision, full papers
were retrieved. Full papers of the selected articles were
examined to determine whether they satisfied the criteria
(G.S.) and then confirmed by a second reviewer (P.P.).
The references of all eligible articles including reviews, expert
opinion papers and systematic reviews were manually
searched for potentially eligible publications. During con-
sensus meetings (G.S., P.P., G.J., G.M.), disagreements
of selections were resolved. In addition, we contacted au-
thors of studies to determine whether data on an eligible
subgroup were available.

Data extraction and items

Data were extracted by a single reviewer (G.S.) using a
standard form, and checked by a second reviewer (P.P.).
The data items extracted were as follows: study design,
study start/end dates, length of follow-up, aim of the
study, characteristics of participants (number of children,
gender, age and associated conditions), dose of MTX and
all outcome measures.

Statistical analysis

A meta-analysis was conducted to determine a combined
estimate of the proportion of children in the eligible stu-
dies responding to MTX. The effect measure for each
study was the proportion of participants classified as re-
sponders on MTX, with respect to intraocular inflamma-
tion [p(i)], where i refers to study i. If not provided in the
original manuscript, we calculated a 95% CI for the observed proportion. We tested for heterogeneity between the effect estimates from studies by conducting Cochrane’s χ² test, which has k – 1 degrees of freedom, where k is the number of studies. In combining estimates, each study estimate was given a weight as the inverse of the proportion variance [i.e. n(i)/p(i)[1 – p(i)] for study i], where n(i) is the number of persons in study i. The combined estimate (p) and its standard error were then calculated in order to provide a 95% CI for this combined estimate of the proportion of patients improving.

Results
A total of 246 articles were identified by searches of databases, and, from these, 194 were excluded by examination of their titles and abstracts. Excluded studies were mainly studies not reporting paediatric cases, duplicates, studies on diseases other than autoimmune non-infectious uveitis, studies on overall mortality among patients receiving immunosuppressive treatment and studies on drugs other than MTX. Full text of the remaining 52 studies and 20 additional papers obtained by screening of their references were scrutinized. From the selection process, a total of nine relevant articles were deemed eligible. The other 63 potential eligible papers were excluded because they were reviews and/or expert opinion papers, they had no information regarding MTX efficacy as single immunosuppressive therapy, it was not possible to extract data on children from an overall study population and this was not available from authors, they did not include data on the principal outcome and/or were non-adherent to SUN criteria.

Table 1 summarizes data items from each eligible paper. All of the included studies were retrospective chart reviews, with a median follow-up time of 22.5 months (range 1-96). The number of children in these studies ranged from 3 to 28, providing a total of 135 children. It was not possible to extract detailed childhood descriptive data from some of the included studies: regarding gender from three studies [6, 9, 11] and age at uveitis onset from one [11]. Twenty-three subjects were male, 46 were female, and the median age of uveitis onset was 8 years (range 1.8–16). Chronic uveitis was associated with JIA (n = 121), early-onset sarcoidosis (n = 5) and tubulointerstitial nephritis (n = 3); the remaining were idiopathic. Six of the nine studies, with a total of 119 patients, were exclusively in JIA patients. Four studies reported a MTX dose between 7.5 and 30 mg/m², weekly, with 15 mg/m² the most commonly used dose. Four studies did not report the dose per m² of body surface and the MTX dose varied from 7.5 to 40 mg/week (median dose/week 12.5 mg); in one study MTX was administered at a dose of 0.5–1 mg/kg, weekly [13].

All included studies reported our main outcome measure: the improvement of intraocular inflammation as Tyndall (anterior chamber cells), according to the definition of improvement of the SUN working group criteria. Altogether, 95 children out 135 included responded to the treatment. The pooled analysis suggested that MTX has a favourable effect in the improvement of intraocular inflammation: 0.73 (95% CI 0.67, 0.81) was the combined estimate of the proportion of subjects improving on MTX (Fig. 1), and there was no evidence of heterogeneity across studies (P = 0.5). In a subanalysis including only those studies exclusively on JIA the estimate was very similar (0.74, 95% CI 0.67, 0.82).

Not all of the secondary outcome variables were present in each study and often were reported in diverse ways; thus we were not able to perform effect size analyses on these. All eligible papers, except Samson et al. [11], which did not report separate childhood data, had information regarding MTX discontinuation: MTX was discontinued in 35 (32.7%) out of 107 children, due to persistent remission in 21 (19.6%), lack of efficacy in 7 (6.5%) and adverse events in the remaining 7. Time to remission on MTX was described in 5 [5–7, 9, 12] out of 9 eligible papers: 45 (73.8%) out of 61 children obtained remission over a median time of 3.5 months (range 1–12). In addition, Foeldvari et al. [7] along with Weiss et al. [13] reported that 25/29 children remained on remission on MTX for a median time of 10.6 months (range 3–27). However, Heiligenhaus et al. [6] reported that remission as per SUN criteria was not obtained in any of the patients during a follow-up period of 27.6 months, and Foeldvari showed that, after MTX discontinuation, 2 of 6 children experienced uveitis flares 3 and 8 months later [7]. During MTX administration, tapering and/or stopping systemic steroid administration was possible in 22 of 23 children, but data were available from only four papers [5, 6, 8, 12]. Data regarding visual outcome have been reported in three articles [6, 8, 10]: 11 of 13 children (84.6%) showed improvement or stable visual acuity post MTX treatment. We could not extract information from Heiligenhaus study [6] because some of their patients (7 of 35) received MTX along with other immunomodulatory drugs. Among 107 MTX exposed children (data regarding children were not available from Samson et al.’s study [11]), 21 (19.6%) experienced adverse events due to MTX administration: 10 children had gastrointestinal discomfort, mostly nausea, 6 showed elevation of liver enzymes, reversible in 3, the remaining 5 children presented both nausea and increased liver function tests.

Discussion
We have estimated that the overall probability of improvement of intraocular inflammation in children affected by refractory ACU treated with MTX is 73%. The estimates of response were similar across studies, in particular when we considered those studies (6 of 9) that included only patients with JIA. However, several caveats have to be discussed before drawing firm conclusions from our systematic review. We recognize RCTs as the gold standard in assessing drug effectiveness; thus because none are available we acknowledge the generally poor quality of evidence. The majority of eligible studies only included patients with JIA, along with other diseases. However, the small number of the available studies meant we
<table>
<thead>
<tr>
<th>Reference, country</th>
<th>Follow-up</th>
<th>n (male/female)</th>
<th>Age, years</th>
<th>Disease</th>
<th>Dose of MTX</th>
<th>Results/outcomes</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>Kalinina Ayuso et al. (2011) [5], The Netherlands</td>
<td>3.1 years</td>
<td>22 (7/15)</td>
<td>8 (±4.0)</td>
<td>JIA</td>
<td>10-15 mg/m²</td>
<td>Uveitis activity: Improved activity in 18 (82%) patients. Discontinuation of MTX: One patient due to gastrointestinal side effects. One patient due to elevated liver enzymes. Thirteen patients due to persistent remission. Steroid intake: Three of four patients on steroid stopped the intake within 2 months after the MTX treatment. Time for remission on MTX: Fifteen patients achieved remission within 1 year (median = 0.5). Time on remission on MTX: 1.5 years (1 month-3 years)</td>
<td>Eleven patients: Gastrointestinal complaints in 7 Elevated liver enzyme in 2 Combination of both in 2</td>
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<tr>
<td>Heiligenhaus et al. (2007) [6], Germany</td>
<td>27.6 (11-89) months</td>
<td>35 (15/20)</td>
<td>4.1 (1-7) onset arthritis; 4.8 (2-10) onset uveitis</td>
<td>JIA</td>
<td>15 mg/m²</td>
<td>Uveitis activity: Improved activity in 25 (71%) patients. Mean time for uveitis flares up after the treatment: 10.3 (3-25) months. Discontinuation of MTX: One patient due to nausea. Three patients due to lack of efficacy. Time for improvement on MTX: 3.75 (2-11) months. Time on remission without MTX: None achieved remission. Steroid intake: All eight patients on steroid stopped the intake after MTX treatment. Visual acuity: Information available on 66 eyes out of 70 eyes; 91% stable and/or improved. Uveitis complications: No new complication occurred in 20. Progression was observed in 15 others.</td>
<td>Increased liver enzyme, 2 patients, nausea, 1 patient</td>
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<td>Foeldvari and Werk (2005) [7], Germany</td>
<td>2.2 years</td>
<td>25 (11/14)</td>
<td>7.9 (1.25-15.7) onset arthritis; 8 (1.8-9) onset uveitis</td>
<td>JIA</td>
<td>15.6 (10-25) mg/m²</td>
<td>Uveitis activity: Improved activity in 21 (84%) patients. Discontinuation of MTX: Six patients due to persistent remission for 12 months. One patient discontinued due to MTX adverse events. Time for remission on MTX: 4.5 (1-12) months. Time on remission on MTX: 10.3 months (3-27).</td>
<td>One patient</td>
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**Table 1 Continued**

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<tr>
<th>Reference, country</th>
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<th>n (male/female)</th>
<th>Age, years</th>
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<tbody>
<tr>
<td>Malik and Pavesio (2005) [8], UK</td>
<td>22.5 (4-40) months</td>
<td>9 (2/7)</td>
<td>11.9 (7-16)</td>
<td>Six patients with idiopathic uveitis and three with Sarcoidosis</td>
<td>23.8 (17.5-30) mg/ m²</td>
<td>Uveitis activity: Improved activity in 5 (55%) patients. Discontinuation of MTX: None. Steroid intake: All the seven children, taking steroid reduced intake after MTX treatment. Initial dose 18 (10-40) mg/die, final dose 2.85 (5-7.5) mg/die. Visual acuity: Improved or stable in all patients.</td>
<td>Nausea, 2 patients</td>
</tr>
<tr>
<td>Kaplan-Messas et al. (2003) [9], Israel</td>
<td>21.5 months (+12.6)</td>
<td>10</td>
<td>3-16</td>
<td>JIA</td>
<td>10-15 mg/week</td>
<td>Uveitis activity: Improved activity in 5 (50%) patients. Discontinuation of MTX: Three patients due to side effects. Two patients due to lack of efficacy.</td>
<td>Nausea/vomiting, elevated liver enzymes, 3 patients</td>
</tr>
<tr>
<td>Gion et al. (2000) [10], USA</td>
<td>19.6 months (6-34)</td>
<td>3 (2/1)</td>
<td>13 (13-15)</td>
<td>TINU</td>
<td>7.5-12.5 mg/week</td>
<td>Uveitis activity: Improved activity in 2 (87%) patients. Discontinuation of MTX: One patient-due to lack of efficacy. Steroid intake: Discontinued in the two patients in whom activity improved.</td>
<td>Abdominal pain, 1 patient</td>
</tr>
<tr>
<td>Samson et al. (2001) [11], USA</td>
<td>16.4 months (1-96)</td>
<td>21</td>
<td>-</td>
<td>JIA</td>
<td>12.3 (7.5-40) mg/week</td>
<td>Uveitis activity: Improved activity in 12 (59%) patients. Steroid intake: Improved activity in two patients. Discontinuation of MTX: None.</td>
<td>No adverse events</td>
</tr>
<tr>
<td>Shefety et al. (1999) [12], USA</td>
<td>28.6 months</td>
<td>4 (1/3)</td>
<td>10.5</td>
<td>2 JIA 2 Sarcoidosis</td>
<td>7.5-12.5 mg/week</td>
<td>Uveitis activity: Improved activity in two patients.</td>
<td>-</td>
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<tr>
<td>Weiss et al. (1998) [13], USA</td>
<td>10 months (6-12)</td>
<td>6 (-/6)</td>
<td>7 (4-14)</td>
<td>JIA</td>
<td>0.5-1 mg/kg/week</td>
<td>Uveitis activity: Improved activity in five patients. Discontinuation of MTX: One patient due to lack of efficacy.</td>
<td>Reversible liver toxicity, 2 patients</td>
</tr>
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</table>

MTX treatment in childhood chronic uveitis
could not consider results separately according to the underlying disease. We did not include studies when it was not possible to extract information on eligible children from those studies (e.g., a study of Behçet’s disease [14]). This affected several large studies on this topic—e.g., Yu et al. [15]. We contacted authors to determine whether information was specifically available on children to allow the study to be included, but this did not result in any additional study being eligible. The main outcome measure used in this systematic review might be considered another limitation: the definition of improvement of the SUN working group criteria [4] is not assessed in childhood, and therefore not validated for childhood use. However, it is otherwise the only standardized measure available for assessing differences in uveitis inflammation, and thus to date, the only item able to compare different studies, across different decades and different childhood diseases. The different steroid use, as systemic administration rather than eye drop, significantly changed over the considered time period, might be an additional potential caveat.

There are no clear recommendations for MTX use in childhood, even though it is largely used in chronic uveitis, mostly when associated with JIA [2, 3, 16–20]. The results of this review could be helpful for clinicians in judging the utility of this treatment and its effect size on visual prognosis, as well as making a therapeutic decision based on current available evidence. Our findings support the clinical use of MTX for refractory ACU in children. However, it needs to be considered in the context that all the current evidence is from retrospective chart reviews. The results of this meta-analysis should prompt the conduct of RCTs on this topic, involving paediatric rheumatologists, ophthalmologists and pharmaceutical companies, to provide a higher quality evidence base.

Rheumatology key messages

- There are few cumulative data on treating children with chronic uveitis.
- MTX seems an effective therapy for childhood non-infectious uveitis associated with JIA and possibly other conditions.
- Randomized clinical trials in childhood ACU treatment seem mandatory.

Disclosure statement: G.T.J. has received grants/research support from Pfizer Inc, NY, USA. All other authors have declared no conflicts of interest.

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