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Methotrexate for uveitis associated with juvenile idiopathic arthritis: Value and requirement for additional anti-inflammatory medication

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PURPOSE. *To study the value of methotrexate (MTX) and the requirement for additional anti-inflammatory drugs for the treatment of severe chronic iridocyclitis associated with juvenile idiopathic arthritis (JIA).*

METHODS. *Institutional study of 35 consecutive patients with JIA started on MTX as the single systemic immunosuppressive drug for the treatment of associated iridocyclitis. The clinical epidemiologic data, course of visual acuity (VA), development of complications, and the need for additional anti-inflammatory drugs were analyzed.*

RESULTS. *Mean follow-up with MTX treatment was 27.6 months. Uveitic complications were present in 31 patients before MTX treatment. With MTX, quiescence of uveitis was obtained with (n=21) or without (n=4) additional topical steroids. Additional systemic immunosuppressive drugs were required in another 7 patients: cyclosporine A (n=4), azathioprine (n=1), infliximab (n=1), or etanercept (n=1). Three patients had active uveitis at the end of the follow-up period. During MTX therapy, uveitis first developed in the unaffected fellow eyes in 2 patients, and secondary glaucoma or ocular hypertension occurred in 7 patients. The VA deteriorated in 6, improved in 13, and was stable in the remaining eyes.*

CONCLUSIONS. *The data suggest that MTX is very effective in controlling inflammation of uveitis in patients with JIA. However, additional topical steroids or systemic immunosuppressive drugs are often required. (Eur J Ophthalmol 2007; 17: 743-8)*

KEY WORDS. *Childhood, Immunosuppression, Juvenile idiopathic arthritis, Methotrexate, Uveitis*

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is frequently associated with iridocyclitis. It is well known that a chronic course of disease may eventually lead to severe visual deterioration as a result of chronic intraocular inflammation (1, 2). Visual loss typically occurs in early onset of the disease, and when glaucomatous optic disc, cataract, or severe inflammation with posterior synechiae is present at the initial presentation. Previous observations suggest that an aggressive and early approach of treatment with the use of immunosuppressive drugs may improve the final outcome.

Methotrexate (MTX) is a potent folic acid antagonist that is an effective treatment for children with idiopathic arthritis (3). Although commonly used for the treatment of uveitis associated with JIA, there are few retrospective case series that investigate the effect of MTX on JIA-associated uveitis (4-9). Furthermore, the previous reports differ with respect to involvement of ophthalmologists for the evaluation of anterior chamber inflammation and the classification of inflammation and remission used. In addition, the value of MTX and additional topical and systemic anti-inflammatory medications has not been addressed in larger case series.

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In the present study, MTX was started as the sole systemic immunosuppressive drug for the treatment of chronic uveitis and was evaluated for its efficacy to improve the course of iridocyclitis in patients with JIA. In particular, the need of additional topical and systemic immunosuppressive drugs in order to achieve inflammatory quiescence was analyzed.

METHODS

The data of 35 consecutive patients with JIA-associated uveitis who were treated between 1998 and 2005 with MTX for their chronic uveitis were analyzed retrospectively. No institutional review board approval is required at our institution for retrospective studies. JIA was classified according to the ILAR criteria (10). All patients had onset of uveitis before the age of 16 years. The uveitis classification applied herein is in accordance with the previously published criteria (11). In all patients included, MTX was the only systemic immunosuppressive drug for the treatment of uveitis at the beginning of follow-up. A stepladder approach of anti-inflammatory treatment was followed in all patients. Briefly, treatment was initiated with a trial of topical prednisolone-acetate 1%, and was tapered off slowly within several weeks. When long-term quiescence was not obtained with low-dose topical steroids (≤3 drops daily), MTX application was started. MTX was given at a dosage of approximately 15 mg weekly/m^2 body surface, either orally or subcutaneously. If complete quiescence was obtained, the topical steroids were subsequently reduced to the lowest possible level. If MTX therapy was eventually not effective in obtaining quiescence of uveitis, a second immunosuppressive drug was added. A switch from MTX to another immunosuppressive drug was preferred in the presence of significant MTX-related side effects or the absence of improvement. Selected patients were kept by the rheumatologist on low dose systemic steroids for the treatment of their arthritis.

We analyzed the epidemiologic data, course of visual acuity, development of additional uveitis complications occurring after institution of MTX, need for additional topical corticosteroids, and the need of additional immunosuppressive drugs to achieve quiescence of inflammation. Patients were followed up at 3-month intervals. Ophthalmologic tests included determination of best-corrected visual acuity, slit-lamp examination, tonometry (Goldmann), and ophthalmoscopy. Fluorescein angiography, perimetry, and mERG examinations were performed, as required.

Activity of anterior uveitis was graded by means of anterior chamber cells (12). At least a two-step decrease or increase of the cell grade was considered as improvement or worsening of anterior uveitis, respectively. Absence of anterior chamber cells was considered as inactive disease. Remission was reserved for inactive uveitis for at least 3 months after discontinuing all treatments for eye disease (12).

In this study, the response of active uveitis to MTX was evaluated, and the ability of MTX to maintain inactive disease when tapering down the topical and systemic corticosteroids.

Best-corrected visual acuity and change of >2 lines (improvement or worsening) and occurrence of uveitis complications during and at the end of the follow-up were documented. Ocular hypertension was considered when elevated intraocular pressure >24 mmHg was noted. Glaucoma was diagnosed when glaucomatous disc change or visual field defect was present.

Examination by a pediatric rheumatologist and monitoring for drug-related side effects was also performed. Any untoward side effects from medication were noted. Statistical analysis was performed with the SPSS program (version 10.0).

RESULTS

The epidemiologic data are summarized in Table I. All of the patients had been on topical corticosteroids at the initial presentation of the study. As a chronic course of anterior chamber inflammation was present in all of the patients, MTX was initiated as the single immunosuppressive drug. In 31 of the cases, one or more uveitis complications were already present at the beginning of the follow-up (Tab. II). The most frequent complications noted were posterior synechiae, cataract formation, and band keratopathy.

It is noteworthy that improvement of inflammation in the anterior chamber was obtained in 32 out of 35 patients treated with MTX (Tab. III). In four patients, this was achieved with MTX monotherapy, and in others, additional topical steroids were needed. It is noteworthy that the steroid eyedrops could be tapered down from ≥4 applications daily before the MTX therapy to less than 3 times after institution of the drug. Eight patients had topical and systemic steroids in addition to MTX. In these patients,

TABLE I - TREATMENT OF CHRONIC UVEITIS WITH METHOTREXATE IN 35 PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA)

Characteristics	No. patients
JIA oligoarthritis, ANA positive	35
Chronic anterior uveitis	35
Female/male	20/15
Onset of arthritis, yr, mean (range)	4.1 (1–7)
Onset of uveitis, yr, mean (range)	4.8 (2–10)
Previous topical steroid therapy	35
Previous immunosuppressive drugs	0

Epidemiologic data at beginning of follow-up.
ANA = Antinuclear antibodies

TABLE II - TREATMENT OF CHRONIC UVEITIS WITH METHOTREXATE IN 35 PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

Characteristics	No. patients/eyes
Best-corrected visual acuity	
≤20/50	20/26
≤20/200	10/12
Complications	
Posterior synechiae	22/34
Cataract formation	19/25
Band keratopathy	18/29
Amblyopia	4/4
Cystoid macular edema	3/4
Dense vitreous opacities	3/3
Glaucoma	1/2
Ocular hypotony	1/1
Strabismus	1/1
Retinal detachment	1/1
Phthisis	0/0

Ocular complications and visual impairment at beginning of follow-up

TABLE III - TREATMENT OF CHRONIC UVEITIS WITH METHOTREXATE (MTX) IN 35 PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

Characteristics	No. patients/eyes
Quiescence of inflammation	32
MTX monotherapy	4
MTX + topical corticosteroids	13
MTX + topical + systemic corticosteroids	8
MTX + other immunomodulatory drugs	7
Remained active	3
New complications occurring under MTX therapy	15
Posterior synechiae	5/5
Glaucoma/ocular hypertension	5/7
Cataract formation	3/3
Cystoid macular edema	2/3
Best-corrected visual acuity	
At any time under MTX therapy	
≤20/50	22/2
≤20/200	7/9
At final visit	
≤20/50	22/28
≤20/200	5/6

Improvement of anterior chamber inflammation during MTX therapy.
Mean follow-up 27.6 months (range 11–89)

the low-dose systemic steroid medication (≤0.1 mg/kg) was continued by the pediatric rheumatologist for treatment of the arthritis.

In another seven patients, the uveitis was still active after 12 weeks of MTX therapy, and the steroid eyedrops were to be continued at ≥4 applications daily. Therefore, cyclosporine A was added as a second immunosuppressive drug in four patients, and azathioprine, etanercept, and infliximab were added in one patient each. By this, an improvement of anterior chamber inflammation and a reduction of the dosage of steroid eye drops was obtained in all of these patients.

Improvement of anterior chamber inflammation occurred after a mean of 3.75 months (range, 2–11). While chronic disease was present before the MTX therapy, mean time to flare-up of uveitis was 10.3 months (range, 3–25) after institution of MTX. However, subsequent recurrence was noted in all of the patients in this study although on sustained immunosuppression. Then, the MTX dosage was adjusted to the actual body weight that had been increased in the meantime, and the recurrence was treated with short-term increase of the topical steroid dose.

Taken together, 32 out of 35 patients had an improvement of iridocyclitis with MTX treatment continued during the follow-up time of 27.6 months (mean, range 11–89). Remission, as defined by inactive disease for 3 or more months after discontinuation of all medication, was not obtained in any of the patients during the follow-up period. Although a second or third immunosuppressive drug was added to MTX, uveitis remained active in 3 children, and improved only after a switch of MTX to other immunosuppressive drugs.

Although uveitis had improved with MTX in the chronically inflamed eye, 2 patients developed uveitis in the formerly unaffected eye. While in 20 patients (37 eyes) no new uveitis complications occurred within the follow-up period with MTX therapy, progression of posterior synechiae, cystoid macular edema, cataract formation, and glaucoma (by progressive optic disc pathology) or ocular hypertension was observed in others (Tab. III). All of the patients with ocular hypertension and glaucoma had sustained IOP ≥24 mmHg and were treated with glaucoma medication. It is noteworthy that the increased IOPs were noted in eyes that had no active uveitis on MTX. In contrast, the development of new posterior synechiae was always associated with periods of active inflammation.

Information on the course of best-corrected visual acuity (BCVA) was available in 66 out of 70 eyes (Tab. III). Briefly, 48 (71.3%) eyes had no significant change in VA during the follow-up time, while it had increased in 13 (19.7%) eyes and decreased in 6 (9%) of the eyes by >2 lines compared to the beginning of the follow-up period.

Adverse effects were noted in only three patients in this series, including elevated liver enzymes in two and nausea in another, the latter prompting to discontinue the therapy.

DISCUSSION

Although this study was performed retrospectively, it shows that MTX is effective in controlling chronic iridocyclitis in patients with JIA. However, additional topical corticosteroids and/or systemic immunosuppression were often required to improve anterior chamber inflammation. No control of inflammation and progression of uveitis complications were noted in some of the patients.

As early as 1969, Lazar et al reported on a 12-year-old girl with uveitis in presumed Still's disease not responding to previous systemic corticosteroids. With MTX, an improvement of vision, cells and flare were noted (4). In the case series provided by Hemady et al (5), uveitis was controlled in two out of three children with MTX treatment. In the third patient, uveitis failed to respond to a combination of MTX with azathioprine.

Weiss et al (6) used low-dose MTX for the treatment of uveitis in seven children with oligoarticular arthritis. All of the patients already had cataract and synechiae, and five had additional glaucoma. Uveitis improvement and steroid-sparing effect of MTX was noted in six out of seven patients. Topical steroids were continued for the sustained improvement in five out of seven children.

Shetty et al (7) reported about their experience with MTX for the treatment of iritis not controlled with topical and systemic corticosteroids. Two patients had JRA, and another two had sarcoidosis. With MTX therapy, the number of cells in the anterior chamber was reduced, and the steroid dose could be tapered down.

Twenty-one out of 160 patients reported by Samson et al (8) had juvenile rheumatoid arthritis–associated recurrent or chronic uveitis. While 59% were controlled with MTX as monotherapy, 41% of the patients required additional medication or substitution by other drugs in order to induce durable uveitis remission.

Most recently, Foeldvari and Wierk (9) reported on their observations with low-dose MTX treatment for uveitis in 25 JIA patients. In 23 of them, uveitis was the indication for MTX therapy. Improvement of uveitis was seen after a mean of 4 months, but occasionally after 12 months. The mean duration of improvement was 10 months. Of the six patients in whom MTX was discontinued after 12 months of uveitis improvement, four remained stable for 1 to 12 months. The authors concluded that MTX is an effective therapy for JIA-associated uveitis.

Together with our findings, this suggests that MTX is of great help in the management of chronic uveitis in JIA. Our data clearly disclose that it typically takes 3 months or even longer until MTX exhibits its anti-inflammatory effect. This is in accordance with previous observations (9). Consequently, therapy may commonly be started with high dosages of topical corticosteroids that are tapered down during the subsequent months, and even systemic steroids may be used in the presence of posterior pole involvement, e.g., in CME.

It may then be warranted to stop steroids completely to minimize their side effects. However, our data now reveal that additional topical low-dose steroid application is required in many patients treated with MTX in order to maintain quiescence of anterior chamber inflammation. The MTX dosages might be unacceptably high and subject the patient to increased risk of side effects if there is an attempt always to discontinue the topical steroids under MTX therapy. The dosage of topical steroids that may be safe with respect to cataract induction is not well defined. Many uveitis experts suggest that topical steroids might not be continued on the long term at dosages greater than three times daily.

While topical steroids should be preferred for treating uveitis, the arthritis may require systemic steroids. In our case series, low-dose steroids were continued in selected patients for the treatment of the joint disease. The value of low-dose systemic steroids for treatment in JIA iridocyclitis is questionable, but may still lead to untoward side effects.

The data show that some of the MTX-treated patients need additional systemic immunosuppression for the improvement of iridocyclitis. Control of severe uveitis in JIA cases has previously been seen when MTX was combined with cyclosporine A and prednisolone (13). Also, combinations with azathioprine, TNF-alpha inhibitors, or other immunosuppressive drugs might be chosen (14-16).

Although on MTX, a group of our patients developed new complications from uveitis as a result of chronically active disease, e.g., posterior synechiae, cataract formation, cystoid macular edema, glaucoma, and ocular hypertension. An influence from previous steroid use on the induction of cataract or elevated intraocular pressure cannot be excluded.

Glaucoma or ocular hypertension appeared in seven of our patients, while the uveitis was under control with the MTX therapy. We can exclude the possibility that we missed severe uveitis flare-ups that might have induced the increased intraocular pressure in our patients, as the follow-up visits were very frequent. It might therefore be speculated that glaucoma resulted from the previous long duration of the chronic inflammation, and the increased secretion of aqueous following control of iridocyclitis in the presence of outflow damage by uveitis.

The observations in this study also suggest that MTX generally must be given for a considerably long time for the treatment of uveitis. Generally, it is required that MTX is maintained for several years. There are currently no data available to form any conclusion about the critical dosage and length of MTX therapy required to obtain long-term quiescence.

MTX is mostly well tolerated. In this study, adverse effects were noted in only three patients. MTX may be preferentially given subcutaneously, as this avoids incomplete absorption from the gastrointestinal tract and may be more effective for the treatment of uveitis.

Immunosuppressive therapy should always be adjusted to the degree of inflammation in the anterior chamber. Therefore, close collaboration between the ophthalmologist and pediatric rheumatologist is mandatory for the care of these patients.

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