Methotrexate Is an Effective Treatment for Chronic Uveitis Associated with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To assess the effectiveness of methotrexate (MTX) in the treatment of juvenile idiopathic arthritis (JIA) associated uveitis, which is still one of the most common causes of visual impairment.

Methods. A retrospective chart review of patients with the diagnosis of uveitis associated with JIA between July 1, 2002, and December 31, 2002.

Results. Four hundred sixty-seven patients with JIA were followed. Thirty-eight had uveitis: 31 associated with oligoarticular JIA and 7 with psoriatic JIA. Twenty-five of the 38 patients received MTX; in 23 patients uveitis was the indication for MTX therapy. In the MTX treated group 46/50 eyes had uveitis, the mean (range) age at onset of uveitis was 7.82 years (1.8–15.8), and the mean age at onset of arthritis was 7.25 years (1.25–15.7). MTX treatment was started an average of 11.4 months (0–72) after the onset of uveitis. The mean MTX dose was 15.6 mg/m^2. Remission occurred after 4.25 months (1–12). Mean duration of remission was 10.3 months (3–27). The total duration of MTX therapy was 661 months and patients were in remission for 417/661 months. In 6 patients MTX was discontinued after 12 months of remission. Four patients were still in remission after 7.5 months (1–14).

Conclusion. MTX seems to be an effective therapy for JIA associated uveitis. (J Rheumatol 2005; 32:362–5)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS	UVEITIS	VISUAL IMPAIRMENT
IMMUNOSUPPRESSIVE TREATMENT	METHOTREXATE	GLUCOCORTICOIDS

Childhood onset chronic uveitis accounts for roughly 10% of all patients with chronic uveitis, and 80–90% of them are associated with juvenile idiopathic arthritis (JIA)[1]. Chronic anterior uveitis is a severe complication of JIA, especially affecting oligoarticular and psoriatic subsets, and still may lead to visual impairment[1-3]. Onset of uveitis before or at onset of arthritis is a risk factor for severe disease[3-6]. Antinuclear antibody positivity[3] and male sex are considered additional risk factors[5].

If there is still an active uveitis after 3 months of local or systemic glucocorticoid therapy[7], immunosuppressive therapy should be initiated. Waheed, *et al* suggest active uveitis, requires immunosuppression with or without chronic steroid use. Currently there are no controlled prospective studies regarding the right choice of immunosuppressive therapy in uveitis associated with JIA. In a pilot study, Weiss, *et al*[8] showed that subcutaneous MTX at a dose of 0.5–1.0 mg/kg once a week was effective for steroid resistant uveitis. In a retrospective case study of MTX, Samson, *et al* observed effectiveness in the treatment of autoimmune uveitis[9] in a larger adult cohort.

We reviewed all our regular patients with steroid resistant uveitis treated with MTX to assess the effectiveness of this therapy.

MATERIALS AND METHODS

Patients. We undertook a retrospective chart review of patients followed in our pediatric rheumatology clinic, a tertiary center for pediatric rheumatology for a recruitment area of about 6 million people, with the diagnosis of uveitis associated with JIA between July 1, 2002, and December 31, 2002. Epidemiologic data, clinical characteristics, response to treatment, and disease course with MTX treatment were collected. Remission was defined as no sign of active uveitis without the application of glucocorticoid eye drops or systemic glucocorticoids during the ophthalmologic examination. The mostly commonly used steroid eye drops were prednisolone acetate (1–0.12% solution).

Ophthalmologic examination. Ophthalmologic examinations were performed according to the suggested guidelines of the Section of Rheumatology and Ophthalmology of the American Academy of Pediatrics[10]. Patients developing uveitis were followed more frequently, as determined by the consultant ophthalmologist according to disease activity. The recruitment area of the tertiary clinic is quite large and because of travel constraints, patients were followed by their local ophthalmologists.

RESULTS

During our period of review, we followed 467 patients with JIA (Figure 1). Thirty-eight had uveitis (Table 1): 31 with oligoarticular JIA and 7 with psoriatic JIA (Figure 1). Twenty-four of the patients were female. Twenty-two devel-

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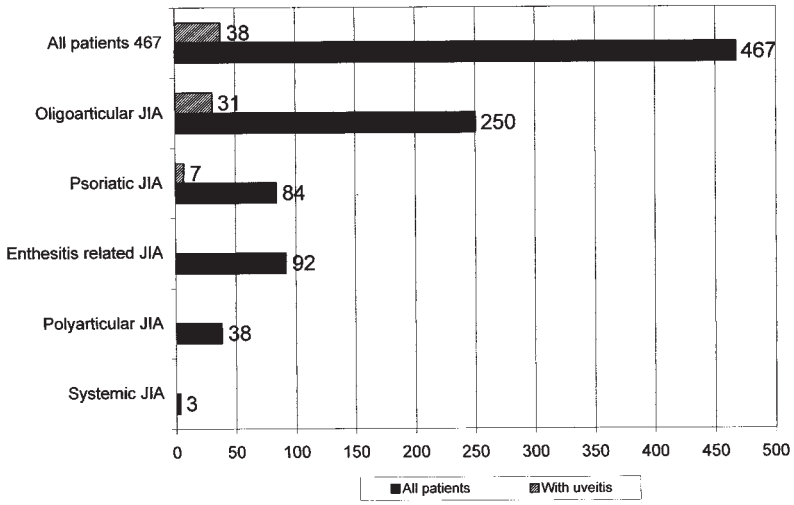

Figure 1. Distribution of patients with uveitis with and without immunosuppressive therapy.

Table 1. Characteristics of patients with JIA.

	All Patients, n = 38	No MTX, n = 13	MTX, n = 25
Sex F/M	23/15	9/4	14/11
Patients with arthritis before uveitis, n (%)	16 (42)	10 (77)	6 (32)
Onset of uveitis at or before diagnosis of arthritis (%)	22 (58)	3 (23)	19 (68)
Mean [median] age at disease onset, yrs (range)	7.59 [7.25] (1.25–16.6)	7.26 [5.25] (1.25–16.6)	7.8 [7.41] (1.25–15.6)
Mean [median] age at onset of uveitis, yrs (range)	7.82 [7.55] (1.81–15.8)	7.60 [7.17] (3.0–15.8)	7.5 [7.33] (1.8–15.5)
No. of involved eyes	64/76	18/26	46/50
Oligoarticular JIA	31	10	21
Psoriatic JIA	7	3	4
Intraocular surgery (%)	8 (21)	1 (7.6)	7 (25)
ANA positive patients, n (%)	20 (49)	8 (61)	12 (42)

MTX: methotrexate.

oped uveitis at or before diagnosis of JIA. In 13 patients uveitis was steroid-sensitive and responded to local or systemic glucocorticoid treatment within 3 months; out of 781 cumulative months of followup, these patients were free of uveitis for 746 months. Twenty-five of the 38 patients with uveitis received MTX; in 23, uveitis was the indication for MTX therapy (Figure 1). In 19 of these 25 patients uveitis was present at time of diagnosis of JIA. In the MTX treated group, 46/50 eyes had uveitis, the mean (range) age at onset of uveitis was 8 years (1.8–9) and the mean age at onset of arthritis was 7.9 years (1.25–15.7). MTX treatment was started an average 11.4 months (0–72) after the onset of uveitis. The mean MTX dose was 15.6 mg/m^2 (10–25); the oral dose of MTX was up to 15 mg/m^2 and the subcutaneous or intramuscular dose was over 15 mg/m^2. Remission occurred the first time after a mean of 4.25 months (1–12). The mean duration of first remission was 10.3 months (3–27). Patients were in remission for 417 months of the 661 months of the total duration of MTX therapy. One patient was switched to leflunomide therapy because of side effects related to MTX treatment. MTX was discontinued when 12 months of continuous remission was reached; 6 of the 28 patients with MTX monotherapy reached this endpoint. Four of these patients were still in remission for both uveitis and arthritis 7.5 months after discontinuation of MTX (1–14 months). Two patients experienced uveitis flares after 3 and 8 months when they were not taking MTX, and MTX was restarted.

Four of the 25 patients did not show any significant improvement from MTX treatment; for 3 of these patients with involvement of 4 of 6 eyes, etanercept was added. Etanercept was started a mean of 18 months (3–72) after initiation of MTX. The mean subcutaneous etanercept dose was 0.42 mg/kg (0.4–0.47) twice a week. All 3 patients responded to treatment with no side effects and remission occurred in 2.5 months (1–3). In one patient etanercept was

discontinued after 12 months' remission, and this patient was still well 14 months later. Another patient had an inadequate response to MTX, but the parents declined etanercept therapy. Accordingly, cyclosporin A (CSA) was added at a dose of 3 mg/kg, and the patient's uveitis stabilized using this combination.

DISCUSSION

In our retrospective chart review 38 (8%) of the 467 patients with JIA had uveitis. This reflects the current reported occurrence of uveitis of about 10% of JIA patients[6]. Uveitis occurred in our cohort in the oligoarticular and the psoriatic subset, but not in the enthesitis related arthritis group. Interestingly, 28 of 38 patients with JIA associated uveitis required MTX therapy, which might represent a bias of our tertiary referral center, where patients referred by ophthalmologists may have more severe uveitis. In 58% of patients the uveitis was present at or before diagnosis in our pediatric rheumatology clinic; this was also true for 68% of patients who required MTX for disease control. This observation of more severe course of uveitis with onset before or concurrent with onset of arthritis has been reported[3-5]. The number of males in the MTX group was 14 of 25, which does not reflect the expected sex distribution of this condition; usually the proportion of males is lower (1:3 or 1:4). This observation overlaps with the observation of Chia, *et al*[11]. Uveitis was the indication for MTX treatment in 23 of 25 patients in the JIA group. MTX treatment was started a mean of 11.4 months after onset of uveitis, mostly because of late referral from ophthalmologists of patients with steroid-nonresponsive uveitis and mild arthritis. Even with such a delay in treatment, 21 of 25 patients responded to MTX, and in 6 patients MTX could be discontinued after 12 months of continuous remission. Remission after institution of MTX treatment occurred after a mean of 4.5 months, which is similar to the time that remission of arthritis in JIA occurs. With 661 months of total observation period under MTX treatment, patients were in remission 63% of the time (417 of 661 months). In comparison, in the non-MTX treated group the total observation period was 781 months and patients were without active uveitis 95% of the time (746 of 781 months). This result does not reflect just a natural fluctuation of the disease course; it shows effectiveness of MTX therapy in patients with more severe uveitis. Our results are similar to the only larger study of MTX treatment in adult patients with uveitis associated with various autoimmune diseases[9]. MTX resulted in disease control in 76% of the 160 patients. The mean dose of MTX was lower in that study at 12.3 mg/week, but in the pediatric population higher doses of MTX are well tolerated and a higher effectiveness can be reached[12].

In 4 patients an additional immunosuppressive medication was needed. In 3 patients etanercept was added and these patients responded within a mean of 2.5 months. Etanercept was discontinued in one patient after 12 months of remission. This promising result has not been noted by others. In the case series of Reiff, *et al*[13] only about 50% of the previously severely therapy-resistant eyes responded. In a small prospective randomized controlled trial of 12 children with uveitis associated with juvenile rheumatoid arthritis (JRA), Smith, *et al*[14] observed that etanercept did not appear to be any more effective than placebo. Data from larger controlled trials are not available. Results of treatment with infliximab, another tumor necrosis factor-α inhibitor, in an open label trial seem to be promising[15], but data from controlled trials are missing for this medication too.

One patient in our cohort was treated with CSA because the parents were concerned about the use of etanercept; the uveitis improved with the combination of MTX and CSA. There are no data on controlled trials of CSA for childhood uveitis. In a larger retrospective case series of 14 children with childhood uveitis, in which only 3 children had JRA associated uveitis, CSA appeared to be effective, but remission occurred only after a mean 25 months of therapy, which we suggest is too long[16].

While MTX seems to be an effective and well tolerated therapy for most patients with JIA associated uveitis, our findings should be confirmed in a prospective randomized controlled trial.

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