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CLINICAL STUDY

Methotrexate: an option for preventing the recurrence of acute anterior uveitis

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Abstract

Aims **To evaluate the efficacy of methotrexate (MTX) in preventing the recurrence of acute anterior uveitis (AAU).**

Methods **This prospective, open, longitudinal study included patients from June 2002 to March 2005 who had either three or more episodes of AAU in the previous year, or a recurrence of AAU within 3 months before starting the trial. We excluded uveitis of infectious origin, masquerade syndromes, and patients with contraindications to MTX. The response criteria were defined as an absence of symptoms and the presence of a normal ophthalmologic examination. The study outcome compared the number of flare-ups of uveitis over an MTX-treated for 1 year to the number of flare-ups of the same group during the previous year without MTX.**

Results **A total of 571 patients with uveitis were evaluated during the period of the study, and 10 fulfilled the inclusion criteria. One patient refused the treatment, and nine completed the study. The mean number of recurrences in the pre-MTX year was 3.4 (SD: 0.52), which was significantly reduced to 0.89 (SD: 1.17) in the year of treatment ($P = 0.011$).**

Conclusion **MTX treatment seems to reduce the number of flare-ups in patients with recurrent AAU.**

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Introduction

Acute anterior uveitis (AAU) is the most common form of uveitis, and it is frequently associated with the HLA-B27 haplotype and spondyloarthritis.[1,2] These patients with uveitis usually respond well to local topical treatment, and systemic drugs are usually not necessary.[3,4] However, it has been reported that 34% of patients with uveitis have AAU that recurs in either a variable period of time or after completion of topical corticosteroid taper.[1,2] In these cases, a benign disease, such as AAU can produce long-term pharmacological mydriasis, deleterious effects of chronic treatment with topical steroids, and complications due to the recurrent flare-ups of uveitis itself. There is no agreement on how to manage these patients, but treatment with disease-modifying antirheumatic drugs could be an option. The literature on the prevention of AAU recurrences is scarce, but one retrospective study showed that treatment with sulfasalazine (SSZ) can reduce the number of AAU recurrences in patients receiving this drug for manifestations related to spondyloarthritis.[5] This was later confirmed in two prospective studies in patients with both spondyloarthritis and idiopathic AAU.[6,7] These studies confirm that the disease-modifying drugs can be an option to prevent the recurrence of AAU.

Methotrexate (MTX) has been used to treat chronic anterior, intermediate, or posterior uveitis,[8–10] but its potential therapeutic benefit in the prevention of AAU flare-ups is unknown. MTX could have some advantages over other disease-modifying antirheumatic drugs (like SSZ), mainly due to the improved efficacy and ease of use for the patients. In patients with rheumatoid arthritis, there are several reasons to choose MTX as the preferred starting therapy, and some of these reasons may apply to patients with uveitis. For example:

- More patients are likely to be taking MTX than any other non-biologic therapy 2–5 years after it is first prescribed.[11]

- MTX acts relatively quickly after being started.[12]
- Doses can be escalated over time, from oral 7.5 mg once weekly to more than 25 mg subcutaneously. These dosing options achieve efficacy without a parallel increases in toxicity. For SSZ, 2–3 g per day are typically required to achieve efficacy, and more than 3 g per day often produces adverse events.[13]
- MTX suppresses disease activity in patients with rheumatoid arthritis in whom other therapies have failed.[14]
- As mentioned before, MTX has demonstrated efficacy in patients with more severe forms of uveitis.[8–10]

Our objective was to evaluate the 1-year efficacy of MTX in the prevention of AAU recurrence.

Patients and methods

Study design

To evaluate the efficacy of MTX in controlling uveitis recurrence, we undertook an open, uncontrolled clinical trial in two centres. The study follow-up period was 1 year.

Patient selection and recruitment

The inclusion criteria for the study were the presence of three or more flare-ups of AAU in the previous year, or a recurrence within 3 months of a previous one. We excluded patients with infectious or malignant uveitis (masquerade syndromes) as well as those with contraindications to MTX. Patients were selected from June 2002 to March 2005 from two uveitis clinics, where each clinic was composed of a team of ophthalmologists and rheumatologists in two tertiary referral hospitals from Madrid and Toledo (Spain). The patients were diagnosed of AAU by an ophthalmologist according to the classification system of International Uveitis Study Group.[15]

Intervention

MTX was administered on a compassionate basis according to the guidelines of the Spanish Health Authorities. Patients provided signed informed consent documentation.

The patients were started on MTX at a dose of 7.5 mg per week, taking folic acid the day after each MTX dosage. When a new flare-up occured, the dose was increased by 5 mg per week up to a maximum of 20 mg. Flare-ups were treated with the local standard treatment, namely topical drops of corticosteroids and mydriatics, or cycloplegics. These topical agents were stopped after the flare-up resolved, and they were not given in any case other than a recurrence of the AAU. No patients received treatment with oral corticosteroids or any disease-modifying drug other than MTX at any time during the study.

Study visits and outcome criteria

Patients were seen every 2 weeks until the acute episode resolved and the ocular therapy ceased. All patients in the study were visited monthly after starting MTX during the first 3 months, and trimonthly thereafter. Additionally, patients were instructed to contact the research group if they experienced a new episode of uveitis. The primary study outcome was the number of recurrences of AAU over a 1-year period of treatment, and this number was compared to the number of such flare-ups in the pretreatment year. The response criteria were defined as the absence of symptoms and a normal ophthalmologic examination.

A new recurrence of AAU was considered to have occured if the patient had symptoms and a physical examination by the opthamologist was compatible with anterior uveitis.

Routine laboratory measurements, including complete blood count and hepatic and renal biochemistry, were performed monthly for the first 3 months and every 8 weeks thereafter.

Statistical analysis

The Wilcoxon's signed-rank test was used to test whether the number of AUU recurrences before and after 1 year of treatment with MTX was different. A sample size of 16 was predetermined to detect a minimum difference of 50% before and after treatment. This design could accept a type I error of 0.05 and a type II error of 0.20, on the basis of our previous uncontrolled experience with MTX.

Results

During the study period, 571 patients attended our specialized uveitis clinics, of which 10 fulfilled the selection criteria. One out of the 10 patients refused the therapy; therefore, nine people completed the study, of which four were men, one had AAU secondary to undifferentiated spondyloarthropathy, and eight had idiopathic AAU. The patient demographics and the number of recurrences before and during the study period are shown in Table 1.

The mean number of flare-ups in the pretreatment year was 3.4 (SD: 0.52, range: 3–4). After 1 year of MTX treatment, the mean number decreased to 0.89 (SD: 1.17, range: 0–3). This difference was statistically significant ($P = 0.011$).

Table 1 Characteristics of the patients included in the study

	Age	*Sex*	*Diagnosis*	*HLA B27*	*Number of flares of uveitis in previous year*	*Number of flares of uveitis during study year*	*Final dose of MTX at the end of the first year (mg per week)*
1	17	Man	Idiopathic AAU	−	4	0	7.5
2	37	Woman	Idiopathic AAU	−	3	3	20
3	50	Woman	Idiopathic AAU	−	4	0	7.5
4	57	Man	Idiopathic AAU	+	4	0	7.5
5	43	Man	Idiopathic AAU	−	3	1	7.5
6	29	Woman	Undifferentiated spondyloarthropathy	+	3	0	7.5
7	50	Man	Idiopathic AAU	+	4	2	17.5
8	47	Woman	Idiopathic AAU	−	3	2	17.5
9	45	Woman	Idiopathic AAU	−	3	0	7.5

Only one patient was considered to be a non-responder; in three patients, the number of recurrences was reduced, and in the remaining five patients, there were no flare-ups during the year of treatment (Table 1). We did not find any relevant adverse effects during the prospective 1 year of follow-up. By protocol, patient number 5 would have needed to increase the dose of MTX to 12.5 mg per week because of a new flare-up. However, this patient had asymptomatic HIV infection, and thus refused to increase the dose of MTX to avoid risks.

Until now, three patients have been treated for more than 3 years, and the other two patients have been treated for more than 2 years, all with good control of the AAU flares. In patients 1, 3, and 4, after 1 year without any flare-up, the dose of MTX was increased because of new recurrences in the second year of therapy. After 6 months without more new flare-ups, the dose was reduced to 10 mg per week in patients 1 and 3, whereas patient 4 continues with a dosage of 17.5 mg per week at the time when this paper was written.

In all five patients that had more than 1 year of follow-up, we detected only two mild adverse events. These were the elevation of transaminases to less than three times the normal values, and these events did not require the patients to stop using MTX or reduce the dose. These two mild adverse effects were resolved by increasing the dose of folic acid given the day after the dose of MTX.

Discussion

MTX has been used to treat severe forms of uveitis, like chronic anterior uveitis, or patients with involvement of posterior or intermediate zone with good results.[8–10] Another retrospective study reports the use of MTX for threatening ocular inflammatory disease in patients with reactive arthritis.[16] To the authors' knowledge, no studies exist in which MTX has been used prospectively to prevent the recurrences of AAU.

For patients with a high recurrence frequency, SSZ has also been demonstrated to reduce the number of flare-ups of idiopathic AAU or those related to spondyloarthritis.[5–7] Furthermore, in those patients on SSZ, new episodes were less severe.[6] However, MTX may have some advantages over SSZ, mainly due to its weekly once administration and high effectiveness. Tellingly, in other diseases that can be treated with either drug, such as rheumatoid arthritis, MTX is considered to be the preferred option for therapy.[11,12,14]

We report a prospective study using MTX, which demonstrated that this drug could prevent recurrences of AAU. The inclusion of patients with three or more flare-ups during a 1-year period was chosen based on the accepted opinion that the occasional flares do not justify treatment beyond topical ocular therapy. However, in patients with three or more episodes of uveitis in 1 year, it would be of interest to minimize the disability that the continuous ocular disease produces.

Our results show that, after starting MTX treatment in patients with three or more episodes in the previous year, the number of recurrences is significantly reduced, with very similar results to those shown for SSZ.[5–7] Out of the nine patients included in this study, only one did not respond, three had a reduction of the number of recurrences, and the remaining five patients had no new flare-ups during the year of treatment with MTX. In addition, five patients still have flare-ups under control after 2 and 3 years of therapy, suggesting that the efficacy can be maintained for a long period of time. Although this is a prospective study, it has the limitations of being open uncontrolled.

In our study, we did not find adverse events during the first year of prospective follow-up. After the second year, only two mild elevations of transaminases were found which resolved after increasing the prophylactic dose of

folic acid. These results are in contrast to the frequent adverse events found by Samson *el al*[8], which obligated to discontinue the drug in 18% of their patients. These adverse events could be explained by the higher doses of MTX used in the Samson's study, up to 40 mg per week, and the coadministration of other drugs like oral corticosteroids, cyclosporine, hydroxychloroquine, or leflunomide.

A recent synthesis of the literature suggests that the incidence of AAU among ankylosing spondylitis patients is reduced by treatment with the tumour necrosis factor (TNF) alpha blockers, mainly anti-TNF antibodies.[17–19] However, the high cost of these agents and the high frequency of infections that accompany them rarely justify their choice as a first-line therapy in patients with AAU. MTX could be an option before administering TNF blockers for those patients with refractory AAU. It is comparable in effectiveness to SSZ, but with a more comfortable use due to its weekly administration and broader range of doses.

In conclusion, our results show that MTX seems to decrease the number of recurrences of AAU over a 1-year period in selected patients. To confirm these preliminary results, controlled clinical trials are warranted.

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