Arch. Immunol. Ther. Exp. (2017) 65:93–97
DOI 10.1007/s00005-016-0402-1

SHORT COMMUNICATION

High Efficacy of Methotrexate in Patients with Recurrent Idiopathic Acute Anterior Uveitis: a Prospective Study

Artur Bachta[1] · Bartłomiej Kisiel[1] · Mateusz Tłustochowicz[2] · Anna Raczkiewicz[1] · Marek Rękas[2] · Witold Tłustochowicz[1]

Received: 14 October 2015 / Accepted: 21 February 2016 / Published online: 11 May 2016

Abstract To evaluate prospectively the efficacy of methotrexate (MTX) in the treatment of recurrent idiopathic acute anterior uveitis (RIAAU). Nineteen out of 22 RIAAU patients completed the study (two patients withdrew their consent shortly after study initiation, one patient discontinued after 4 weeks because of the adverse effects). All patients were treated with MTX in a starting dose of 15 mg/week, increased to target dose of 25 mg/week after 4 weeks. In patients taking systemic corticosteroids (CS) the dose was gradually tapered (by 2.5 mg every week) until discontinuation. The mean follow-up period was 3.3 years (19–59 months). Sixteen patients (84 %) remained flare-free on MTX therapy. In the remaining three patients the mean interval between flares increased from 4.8 to 18.3 months. Systemic CS were tapered off in all patients. The number of acute anterior uveitis flares in the whole cohort decreased from 2.12 to 0.11/patient-year ($p < 0.0001$). All flares observed on MTX therapy occurred in HLA-B27-positive patients. MTX dosed at 25 mg/week is highly effective in the treatment of RIAAU.

Keywords Uveitis · Inflammation · Immunotherapy · Methotrexate

✉ Artur Bachta
artur.bachta@gmail.com

[1] Department of Internal Diseases and Rheumatology, Military Institute of Medicine, Warsaw, Poland

[2] Department of Ophthalmology, Military Institute of Medicine, Warsaw, Poland

Introduction

Uveitis is a set of conditions characterized by the inflammation of the uvea. The overall incidence of uveitis varies from 14 to 52.4/100,000 in the general population (Chang and Wakefield 2002; Dandona et al. 2000; Darrell et al. 1962). It is classified as anterior, intermediate, posterior or panuveitis, depending on the part of uvea affected. Acute anterior uveitis (AAU) is the most common form accounting for 75–90 % of cases in Western Countries (Chang and Wakefield 2002).

Uveitis is a heterogeneous group of diseases with complex pathogenesis. In general, two major forms can be distinguished: infectious and non-infectious uveitis. Non-infectious (or autoimmune) uveitis may be secondary to several diseases, including systemic autoimmune rheumatic diseases, such as spondyloarthritis and Behçet's disease. However, in many cases no underlying disease can be found and uveitis is considered idiopathic (Selmi 2014).

AAU manifests by redness, periorbital pain, photophobia, and blurred vision. AAU warrants urgent evaluation and treatment to avoid such complications as posterior synechiae, secondary glaucoma and cataract, and macular edema (Selmi 2014).

Most cases of non-infectious AAU respond well to topical corticosteroids (CS) and mydriatic drugs. In more severe cases periocular CS injections or systemic CS are used. In some cases corticosteroid-sparing agents should be considered. Indications for the use of corticosteroid-sparing agents include: the inability to control inflammation with high-dose CS, the inability to control ocular inflammation with a prednisone dose of $\leq$10 mg/day, the occurrence of adverse effects that require tapering or discontinuation of CS (Jabs and Rosenbaum 2001).

Methotrexate (MTX) is one of the most widely used immunosuppressive drugs in uveitis due to its relatively safe profile. Several reports have shown that MTX is effective in the treatment of ocular inflammatory diseases (Bom et al. 2001; Foeldvari and Wierk 2005; Gangaputra et al. 2009; Kaplan-Messas et al. 2003; Muñoz-Fernández et al. 2009; Samson et al. 2001; Shah et al. 1992). However, all these studies had several limitations. Most of them were retrospective, and several studies included only about ten patients or less. On the other hand, large studies like those by Gangaputra et al. (2009), or Kaplan-Mesas et al. (2003) included patients with different types of ocular inflammation. The interpretation of the results was also hindered by the use of different doses of MTX (moreover, the doses of MTX were significantly lower than optimal doses in chronic rheumatic diseases, i.e., 25–30 mg/week) as well as by concomitant treatment with systemic CS and/or other immunosuppressive drugs. To our knowledge, only one small study has prospectively evaluated the efficacy of MTX in preventing the recurrence of AAU (Muñoz-Fernández et al. 2009).

We present the results of a prospective study evaluating the treatment of recurrent idiopathic AAU (RIAAU) with MTX.

Materials and Methods

The study was approved by the institutional ethics committee (Ethics Committee of the Military Institute of Medicine, Warsaw, Poland). Each participant signed an informed consent form. All procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Objectives

The purpose of the study was to evaluate prospectively the efficacy of MTX in the treatment of RIAAU.

Patients

Twenty-two patients with RIAAU were enrolled in the study. The inclusion and exclusion criteria are presented in Table 1. The data concerning previous flares (i.e., before the enrollment to the study) were extracted from the patients records. Two patients withdrew their consent just after enrollment and one patient discontinued the study after 4 weeks because of the adverse effects (persistent nausea and abdominal pain). Thus, 19 patients were finally included in the analysis.

Table 1 Inclusion and exclusion criteria

Inclusion criteria
1. Provided informed consent
2. ≥18 years of age at time of enrollment
3. Recurrent non-infectious acute anterior uveitis (≥3 flares)
4. No history of prior treatment with disease modifying anti-rheumatic drugs
Exclusion criteria
1. Chronic back pain
2. History of arthritis or enthesitis or dactylitis
3. Evidence of systemic autoimmune disease
4. Evidence of malignancy
5. Evidence or recent serious, recurrent or chronic infection, including human immunodeficiency virus, hepatitis B and hepatitis C
6. Severe systemic disease (e.g. renal failure, liver disease)
7. Significant laboratory abnormalities
Aspartate aminotransferase or alanine aminotransferase >2 × the upper limit of normal
Creatinine >the upper limit of normal
White blood cell $<3\times10^3/\mu L$
Hemoglobin <10 g/dL
Platelets $<100 \times 10^3/\mu L$
8. Evidence of psychiatric disorder or substance abuse
9. Pregnant or nursing women
10. Women of child-bearing potential unwilling to use effective contraception during the study

Treatment Protocol

MTX therapy was started at oral dose of 15 mg/week and increased to 25 mg/week after 4 weeks. Folate at a dose of 15 mg/week was added in all patients to minimize any adverse effects. In five patients taking systemic CS at baseline the dose (of CS) was gradually tapered (by 2.5 mg every week) until discontinuation.

The first follow-up visit was 4 weeks after the therapy initiation and every 3 months thereafter. Ophthalmologic examination and laboratory tests (complete blood count, transaminases, creatinine) were performed at each follow-up visit. Adverse events were also investigated. Patients with AAU flares were advised to come in between regular visits. All AAU flares were treated with topical CS and mydriatic drugs (no systemic treatment with CS was used).

Treatment Outcomes

The frequency of flares before and after the initiation of MTX therapy was compared. The frequency of flares was reported as the number of flares per patient-year.

Statistical Analysis

All statistical tests were performed with STATISTICA 10.0 (StatSoft). The age, sex, percentage of HLA-B27-positive patients, duration of observation and follow-up, and number of flares were tabulated. Means and standard deviations were calculated. The recurrence rate was expressed as number of flares per patient-year. The Wilcoxon signed rank test was used to compare recurrence rates before and after treatment. A p value less or equal to 0.05 was considered significant.

Results

Nineteen patients with RIAAU were included in the analysis. The mean age was 38.6 years (±14.3) and was similar in HLA-B27-positive and HLA-B27-negative patients (38.6 ± 8.4 vs. 38.5 ± 17.3 years; $p > 0.05$). Eleven out of 19 patients (57.9 %) were males. Unilateral disease was defined as the involvement of only one eye. Patients with simultaneous or alternate involvement of both eyes were classified as having bilateral disease. Thirteen patients (68.4 %) were classified as having unilateral disease. No significant differences were found between the sexes either in baseline characteristics or in outcomes.

Time of follow-up (from MTX therapy initiation to the last visit) was at least three times longer (12.39 times longer on average) than the interval between AAU flares before MTX therapy initiation in each patient.

We observed a significant decrease of AAU flares during MTX therapy (2.12 vs. 0.11/patient-year; $p < 0.0001$) (Table 2). This beneficial effect was observed in both HLA-B27-negative and HLA-B27-positive patients (Table 2). A total of seven AAU flares occurred in three patients (four flares in one patients, two flares in one patient and one flare in one patient). However, the mean interval between flares increased from 4.8 months before MTX initiation to 18.3 months on MTX treatment. All AAU flares observed on MTX treatment occurred in HLA-B27-positive patients. Sixteen patients (84 %) remained flare-free during the follow-up (Fig. 1).

Methotrexate side effects were observed in five patients: transient hypertransaminasemia in three patients (<2 × the upper limit of normal), periodic episodes of nausea in two patients, transient fatigue in one patient, abdominal distension in three patients. All adverse effects were mild and did not lead to MTX withdrawal.

Five patients were treated with prednisone at baseline. CS were tapered off completely by the third month of MTX treatment.

Discussion

MTX is one of the most commonly used immunosuppressive drugs in ocular inflammation. Several studies showed its efficacy in different entities, idiopathic as well as secondary to systemic autoimmune diseases.

A retrospective study by Foeldvari and Wierk (2005) suggested that MTX may be an effective therapy in juvenile idiopathic arthritis associated with chronic uveitis. The study group comprised 25 patients treated with MTX in a mean dose of 15.6 mg/m^2/week. Shah et al. (1992) reported a good clinical response of different inflammatory ocular diseases (including nine patients with uveitis) to low doses of MTX. Kaplan-Messas et al. (2003) retrospectively analyzed the results of MTX therapy in 39 patients with uveitis and scleritis (including 20 patients with idiopathic uveitis). MTX was discontinued in ten patients due to

Table 2 Treatment outcome

	Time of observation [years] mean (SD)	Observation [patient-years]	Number of AAU flares	Number of AAU flares per patient-year
All patients ($n = 19$)	2.75 (2.66) vs. 3.33 (1.24)	52.31 vs. 63.23	111 vs. 7	2.12 vs. 0.11
Before study initiation (from first AAU flare to MTX therapy initiation) vs. after study initiation (from MTX therapy initiation to last follow-up visit)				$p < 0.0001$
HLA-B27 positive ($n = 8$)	2.55 (2.63) vs. 4.00 (0.96)	20.42 vs. 32.00	42 vs. 7	2.05 vs. 0.21
Before study initiation (from first AAU flare to MTX therapy initiation) vs. after study initiation (from MTX therapy initiation to last follow-up visit)				$p < 0.0001$
HLA-B27 negative ($n = 11$)	2.90 (2.66) vs. 2.84 (1.20)	31.89 vs. 31.23	69 vs. 0	2.16 vs 0
Before study initiation (from first AAU flare to MTX therapy initiation) vs. after study initiation (from MTX therapy initiation to last follow-up visit)				$p < 0.0001$

AAU acute anterior uveitis, *MTX* methotrexate

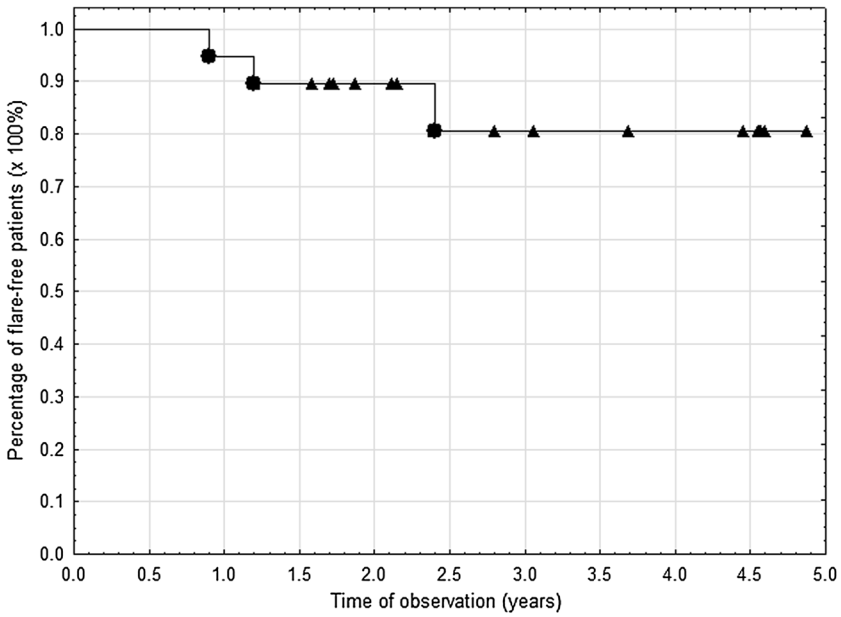

Fig. 1 Kaplan-Meier curve demonstrating overall flare-free survival during follow-up. Censored values (*filled triangle*) indicate the last known follow-up for patients who did not flare. Completed values (*filled circle*) indicate the first flare during follow-up for patients who did flare

adverse effects. Full or partial control of the inflammation was observed in 23 out of 29 patients. Most patients discontinued systemic CS (20 out of 23). A similar response rate (76 %) was found in a large series of patients with chronic uveitis (160 patients, including 58 patients with idiopathic uveitis) (Samson et al. 2001). The mean maintenance dosage of MTX was 12.3 mg/week. However, cyclosporine was added to the regimen in some patients. A steroid-sparing effect was achieved in 64 % of patients (46 out of 72 patients treated with CS). The authors found no statistical significance in the successful control of inflammation with regard to gender, anatomic location, and specific cause. The largest cohort of patients with ocular inflammatory disease on MTX treatment was described by Gangaputra et al. (2009). This retrospective study comprised 384 uveitis patients on MTX therapy (including 126 patients with anterior uveitis). In patients with anterior uveitis a complete remission was achieved in 55.6 % of patients within 6 months and 67.2 % of patients within 12 months, while CS-sparing effect (prednisone $\leq$10 mg/day) in 46.15 % of patients and 62.6 % of patients, respectively.

Our study suggests that MTX is highly effective in the treatment of RIAAU (remission was achieved in 84 % of patients and reduced frequency of flares in 16 % of patients). It should be underlined that the follow-up period was several times longer that the interval between AAU flares before MTX therapy initiation in each patient (12.39 times longer on average). It should be emphasized that MTX was the sole immunosuppressive drug used in our cohort and that systemic CS were discontinued in all patients. Thus, the observed beneficial effect can be attributed completely to MTX therapy. In previous studies patients were treated with different doses of MTX; moreover, some patients continued systemic CS and/or were treated with a combination of two immunosuppressive drugs. Our MTX dose (25 mg/week in all patients) was higher than in most previous studies.

The treatment success rate in our cohort was markedly higher than those in the studies mentioned above. However, our results cannot be compared directly with the results of most of the previous studies. First, our cohort comprised only patients with recurrent AAU while most of the previous studies comprised patients with different types of ocular inflammation. Second, our patients had recurrent acute inflammation while previous studies focused mostly on chronic ocular inflammation. Third, our study was prospective while previous studies were retrospective. Fourth, our study included only patients with the idiopathic form of uveitis while previous studies comprised also patients with ocular inflammation secondary to systemic diseases.

Our study comprised only patients with anterior uveitis. However, when comparing treatment success rates only for anterior uveitis, the results still seem to be better in our cohort. It may be due to different types of anterior uveitis (recurrent acute vs. chronic). A higher MTX dosage in our cohort is another possible explanation.

To our knowledge, the only prospective study evaluating the efficacy of MTX in preventing recurrences of AAU was that by Muñoz-Fernández et al. (2009). The study comprised nine patients (eight with RIAAU and one with

recurrent spondyloarthritis-associated AAU) and the follow-up period was 1 year. Mean MTX maintenance dose was 11.11 mg/week. Five patients (56 %) were flares-free during follow-up, the number of recurrences was reduced in three patients (33 %) and one patient was considered to be a non-responder. We also conducted the analysis of combined data from the two studies [all patients from our cohort and eight patients with RIAAU form the study by Muñoz-Fernández et al. (2009)]. The results of the pooled analysis (2.34 flares per patient-year before the treatment with MTX vs. 0.24 flares per patient-year during the treatment; $p < 0.0001$) confirm the beneficial effect of MTX on RIAAU. However, our results seem to be better than those from the study by Muñoz-Fernández et al. (2009) (84 vs. 50 % of flares-free patients; $p = 0.064$). It can be due to significantly higher doses of MTX in our study (25 vs 11.1 mg/week).

Interestingly, all flares observed during the follow-up occurred in HLA-B27-positive patients. It should be emphasized that only 42 % of patients (8/19) in our study group were HLA-B27-positive. This observation suggests that HLA-B27 might influence the response to MTX therapy. However, this hypothesis has to be confirmed in larger studies.

Severe adverse effects leading to treatment discontinuation occurred only in one patient (the patient was excluded from the analysis because of short follow-up period). Among the remaining patients side effects were mild and/or transient. These results confirm that MTX therapy is safe and generally well tolerated.

In summary, idiopathic AAU usually responds well to topical CS and has a relatively good prognosis. However, recurrent AAU may lead to severe complications (including sight loss). Systemic CS may help to prevent recurrence of AAU but long-term CS therapy is associated with severe adverse effects. Thus, CS-sparing agents should be considered in such cases. Our results show that MTX (in doses considered optimal in rheumatic diseases) is a highly effective and safe therapy for RIAAU.

Acknowledgments Special thanks to Mr. Romuald Zadora-Przyłęcki for help in editing the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interests regarding the publication of this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

Bom S, Zamiri P, Lightman S (2001) Use of methotrexate in the management of sight-threatening uveitis. Ocul Immunol Inflamm 9:35–40

Chang JH, Wakefield D (2002) Uveitis: a global perspective. Ocul Immunol Inflamm 10:263–279

Dandona L, Dandona R, John RK et al (2000) Population based assessment of uveitis in an urban population in southern India. Br J Ophthalmol 84:706–709

Darrell RW, Wagener HP, Kurland LT (1962) Epidemiology of uveitis. Incidence and prevalence in a small urban community. Arch Ophthalmol 68:502–514

Foeldvari I, Wierk A (2005) Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol 32:362–365

Gangaputra S, Newcomb CW, Liesegang TL et al (2009) Methotrexate for ocular inflammatory diseases. Ophthalmology 116:2188–2198

Jabs DA, Rosenbaum JT (2001) Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol 131:679

Kaplan-Messas A, Barkana Y, Avni I et al (2003) Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis. Ocul Immunol Inflamm 11:131–139

Muñoz-Fernández S, García-Aparicio AM, Hidalgo MV et al (2009) Methotrexate: an option for preventing the recurrence of acute anterior uveitis. Eye 23:1130–1133

Samson CM, Waheed N, Baltatzis S et al (2001) Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. Ophthalmology 108:1134–1139

Selmi C (2014) Diagnosis and classification of autoimmune uveitis. Autoimmun Rev 13:591–594

Shah SS, Lowder CY, Schmitt MA et al (1992) Low-dose methotrexate therapy for ocular inflammatory disease. Ophthalmology 99:1419–1423