Methotrexate Therapy May Prevent the Onset of Uveitis in Juvenile Idiopathic Arthritis

Charalampia Papadopoulou, MD[1], Mikhail Kostik, MD[1], Marek Böhm, MD[1,2], Juan Carlos Nieto-Gonzalez, MD[1], Maria Isabel Gonzalez-Fernandez, MD[1], Angela Pistorio, MD, PhD[1], Alberto Martini, MD[1,3], and Angelo Ravelli, MD[1,3]

Objective To evaluate whether early treatment with methotrexate (MTX) prevents the onset of uveitis in children with juvenile idiopathic arthritis.

Study design The clinical charts of all consecutive patients seen between January 2002 and February 2011 who had a disease duration <1 year at first visit and had received a stable management for at least 2 years with or without MTX were reviewed. Patients who were given systemic medications other than MTX (except nonsteroidal anti-inflammatory drugs) were excluded. Patients with systemic arthritis, rheumatoid factor-positive arthritis, or enthesitis-related arthritis were also excluded. In each patient, the 2-year follow-up period after first visit was examined to establish whether uveitis had occurred.

Results A total of 254 patients with a median disease duration of 0.3 year were included. Eighty-six patients (33.9%) were treated with MTX, whereas 168 patients (66.1%) did not receive MTX. During the 2-year follow-up, 211 patients (83.1%) did not develop uveitis, whereas 43 patients (16.9%) had uveitis a median of 1.0 year after the first visit. The frequency of uveitis was lower in MTX-treated than in MTX-untreated patients (10.5% vs 20.2%, respectively, $P = .049$). Survival analysis confirmed that patients treated with MTX had a lower probability of developing uveitis.

Conclusion Early MTX therapy may prevent the onset of uveitis in children with juvenile idiopathic arthritis. Because our study may be affected by confounding by indication, the potential of MTX to reduce the incidence of ocular disease should be investigated in a randomized controlled trial. *(J Pediatr 2013;163:879-84)*.

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic anterior uveitis in childhood,[1,2] and uveitis is the most frequent extra-articular manifestation seen overall in children with JIA.[3] Ocular involvement is strongly associated with a constellation of particular clinical features, which include the presence of antinuclear antibodies (ANA), young age at disease onset, female sex, and an asymmetric pattern of arthritis.[4] Patients with systemic disease or rheumatoid factor (RF)-positive arthritis rarely develop uveitis.

The onset of chronic anterior uveitis is insidious and often entirely asymptomatic, which contrasts with painful, acute iridocyclitis that can be seen in enthesitis-related arthritis.[4] One or both eyes can be affected. Uveitis is discovered in <10% of patients before the onset of arthritis, whereas in most cases the disease occurs in the earlier years after disease presentation.[5] A shorter interval between arthritis and uveitis onset was found to be the main predictor of severe course of uveitis in JIA.[6]

Uveitis is a serious condition and has the potential to cause sight-threatening ocular complications, which include posterior synechiae, band keratopathy, cataract, and glaucoma.[7,8] Prevention of eye morbidity relies very much on early diagnosis and treatment.

Routine implementation of ophthalmologic screening and development of better therapies have led to a marked improvement of prognosis in JIA-related uveitis, with a decrease in the reported rate of visual loss from 22%-66% in studies before 1990 to 3%-25% in recent studies.[3] However, in contrast with the recent improvements in the treatment strategy for arthritis, less progress has been made in the management of uveitis. In particular, no controlled trials have been done.

Methotrexate (MTX) is currently the disease-modifying antirheumatic drug of first choice for the management of polyarthritis in children with JIA, based on the results of 2 randomized controlled trials.[9,10] MTX is also regarded as first-line treatment of uveitis that is severe or refractory to topical or oral corticosteroids,[11] although its effectiveness in ocular disease is only derived from anecdotal interventional studies.[12-14] Recently, further evidence of the therapeutic potential of MTX has been inferred from the observation that a high number of children who achieved remission relapsed quickly after discontinuation of the drug.[15]

ANA	Antinuclear antibodies
IACI	Intra-articular corticosteroid injection
ILAR	International League for Associations of Rheumatology
JIA	Juvenile idiopathic arthritis
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
RF	Rheumatoid factor

From the [1]Istituto Giannina Gaslini, Genova, Italy; [2]Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic; and [3]Università degli Studi di Genova, Genova, Italy

M.B. received the Articulum Fellowships and was supported by the Ministry of Health of Czech Republic (RVO-VFN64165/2012) and Charles University (PRVOUK P24/LF1/3). The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.03.047

A still unanswered question is whether MTX alters the incidence of uveitis in children with JIA.[3] Addressing this issue is important because the demonstration that MTX is able to prevent uveitis might extend its indications to the management of children with oligoarthritis, who have a high prevalence of uveitis but are usually not candidates for MTX therapy, at least at their initial disease stages.[16]

The primary aim of the present study was to investigate whether early treatment with MTX prevents the occurrence of uveitis in children with JIA.

Methods

The study was conducted by review of the charts of all consecutive patients who: (1) met the International League for Associations of Rheumatology (ILAR) criteria for JIA[17]; (2) were first seen at the study center between January 2002 and February 2011; (3) had a disease duration of <1 year at the first observation; (4) had a minimum follow-up duration after the first visit of 2 years; and (5) had received a stable management for at least 2 years after the first visit with either MTX, with or without nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular corticosteroid injections (IACIs) (MTX group) or only NSAIDs or IACIs, without MTX (no-MTX group).

Patients in either group who were given systemic medications other than MTX (eg, systemic corticosteroids, other disease-modifying antirheumatic drugs, or biologic agents) were excluded. The maximum interval of 1 year between disease onset and first visit and the maximum duration of follow-up of 2 years were chosen because in the authors' series the onset of uveitis has been found to peak in the first 2 years after JIA presentation.[5]

Children with systemic arthritis and RF-positive arthritis were excluded owing to the rarity of uveitis in these disease categories. Children with enthesitis-related arthritis were also excluded because uveitis in this JIA category is usually acute and symptomatic. Other exclusion criteria were the development of uveitis before the onset of arthritis or before the first observation at study center or the presence of active uveitis at the first visit.

MTX was administered at 15 mg/m^2/wk (maximum 25 mg/wk) in all patients. The choice of the oral or subcutaneous route of administration depended on the personal preference of the attending physician.

In each patient, the 2-year follow-up period after first visit was examined to establish whether uveitis had occurred. In patients who developed uveitis, the follow-up was censored at the time when uveitis was first diagnosed, whereas in patients who did not have uveitis, the follow-up was censored at the 2-year visit. In case of the occurrence of uveitis, the time interval from first visit to diagnosis of uveitis was recorded.

All patients had received a routine slit-lamp evaluation every 3-4 months. In all, the diagnosis of chronic anterior uveitis was confirmed by an ophthalmologist and was defined according to the Standardization of Uveitis Nomenclature Working Group criteria.[18]

Patients were defined as being ANA positive if they had at least 2 positive results on indirect immunofluorescence at a titer of ≥1:160, as previously reported.[19]

The study was approved by the independent ethics committee of the Istituto G. Gaslini, Genova, Italy.

Statistical Analyses

Descriptive statistics were reported in terms of medians and IQRs for continuous variables and in terms of absolute frequencies and percentages for categorical variables. Comparison of quantitative variables between groups was made by means of the Mann-Whitney *U* test. Comparison of qualitative data was performed by means of the χ^2 test or the Fisher exact test in case of expected frequencies <5. Survival analysis, with first episode of uveitis as the event of interest, in each group was conducted by means of the Kaplan-Meier method. Survival curves were compared by the log-rank test. The software Statistica (release 6.0; StatSoft Corporation, Tulsa, Oklahoma) and Stata (release 7.0; StataCorp, College Station, Texas) were used for data analyses.

Results

A total of 254 patients met the inclusion criteria and were eligible for enrollment in either of the 2 groups. These patients were part of a whole series of ~900 patients with JIA who were seen at the study center during the study period. Table I shows the main demographic, clinical, and treatment characteristics of patients at their baseline visit. Overall, the series was overly represented by girls with early disease onset and positive ANA status.[19] The majority of patients had the ILAR categories of persistent and extended oligoarthritis (61.8% and 22.4%, respectively); 14.2% of patients had RF-negative polyarthritis. As per inclusion criteria, patients had on average a short disease duration (median, 0.3 year).

During the 2-year follow-up, 211 patients (83.1%) did not develop uveitis, whereas 43 patients (16.9%) had uveitis, which was diagnosed a median of 1.0 year (IQR 0.4-1.4 years) after the first visit. The prevalence of uveitis in our series is similar to that recently reported in a large sample of children with JIA.[3] The comparison of demographic, clinical, and therapeutic characteristics of patients who had or did not have uveitis is presented in Table I. Children who had uveitis were comparable with children who did not experience ocular disease for all features, except for a younger age at disease onset, a greater frequency of positivity for ANA, a more common involvement of proximal interphalangeal joints, and a lower frequency of MTX therapy. Regarding ANA, it is worth emphasizing that these autoantibodies were detected in all patients with uveitis but were also present in as many as 90% of patients without uveitis. The percentage of patients who received MTX orally or subcutaneously was comparable in the 2 groups (data not shown).

In the 2-year follow-up period, 86 patients (33.9%) were treated with MTX, whereas 168 patients (66.1%) did not receive MTX. The main demographic, clinical, and treatment characteristics of patients included in the 2 therapeutic