Management of Chronic Noninfectious Uveitis with Low-Dose Methotrexate

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Research Article

Keywords: Methotrexate, Low-dose, Uveitis, Steroid-sparing effect

Posted Date: March 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-161087/v1

Abstract

Purpose

To evaluate the effectiveness of low-dose oral methotrexate(5mg/week) among chronic noninfectious uveitis patients who were unresponsive to conventional steroids therapy.

Methods

27 patients with chronic noninfectious uveitis who were treated with low-dose methotrexate (MTX) at ophthalmology department of Pyongyang University of Medical Science Hospital from 2017 to 2020 were participated in this study.Each patient received oral MTX at dose of 5mg/week except that 2 patients were given 7.5mg/week MTX for the first 4 weeks. The treatment effects were evaluated based on ratio of inflammation control, Log MAR visual acuity, mean number of relapses and steroid-sparing effect. Every adverse effect associated with drug use was recorded.

Results

Control of inflammation was achieved in 92.6% of patients. Visual acuity was improved in 82.9% (29 eyes among 35 eyes) and maintained in 5.7% (2 eyes). The mean number of relapses was decreased from 4.2 (before therapy) to 1.9 (after therapy). Steroid-sparing effect was achieved in 85.2% patients. There was no serious side effect requiring discontinuation of therapy but some adverse reactions were recorded in 22.2% of patients.

Conclusions

Low-dose methotrexate(5mg/week) is supposed to be able to successfully control chronic noninfectious uveitis and has a steroid-sparing effect. It is also safer because it shows less adverse effects.

Introduction

Uveitis is one of the important causes of vision loss worldwide [1-7]. According to etiology, it is divided into 2 groups- infectious and noninfectious uveitis. Generally, it is standard to treat noninfectious uveitis with systemic or topical corticosteroids, but in clinical practice, it is not uncommon to see patients who are unresponsive to steroids alone. Therefore, systemic immunomodulatory therapy (IMT) with oral corticosteroids is currently the mainstay of treatment to control noninfectious uveitis [3].

Methotrexate is a folic acid antagonist, which is frequently used in the field of ophthalmology to control ocular inflammation due to its immunomodulatory function [8-12].Although methotrexate can effectively control uveitis, use of these drugs at high dose for prolonged period carries the risk of systemic side

effects, which even sometimes lead to discontinuation of therapy. Therefore, low-dose MTX therapy is preferable as long as it shows therapeutic effects. Typical dose of oral MTX ranges from 7.5mg to 25mg given once weekly [8, 13-15].

However, we used only 5mg of methotrexate per week for chronic noninfectious uveitis patients and found out it was not only able to control inflammation but also had a steroid-sparing effect. And it also showed less severe side effects.

The purpose of this report is to describe our experience in use of MTX at very low dose of 5mg/week in case series of chronic noninfectious uveitis.

Materials And Methods

Chronic noninfectious uveitis patients treated with low-dose methotrexate at ophthalmology department of Pyongyang University of Medical Science Hospital from 2017 to 2020 were included. Chronic uveitis was defined as intraocular inflammation lasting over 3 months [16]. Classification of “noninfectious uveitis” was based on the absence of infectious causes by the results of the several diagnostic approaches. 27 patients matched the criteria.

Selected patients were given MTX once weekly. Mean dose of methotrexate was 5mg per week except that first 2 patients were given 7.5mg/week for the first 4 weeks.

The patients were followed up at every 4 weeks after initiation of therapy. A complete ocular examination was performed at each visit,including visual acuity, slit-lamp biomicroscopy, tonometry, and ophthalmoscopy. Patients were specifically questioned for adverse reactions associated with MTX. Complete blood count and liver enzymes were reviewed monthly.

Initial and final vision were calculated in Log MAR and the visual acuity changes were evaluated. For patients with anterior uveitis, we supposed that inflammation was controlled if aqueous cell was less than 1+ for over 6 consecutive months, while in the cases with posterior involvement, there should not be any sign of active inflammatory lesions, optic nerve edema, or vasculitis. Steroid-sparing effect was evaluated based on calculation of ratio of patients who discontinued systemic steroids 6 months after the initiation of therapy. The mean number of relapses was estimated by frequency of inflammation recurrence per patient in a year before initiation of MTX therapy and after therapy, respectively.

Results

27 patients with chronic noninfectious uveitis were participated in this study. 14 patients were male and 13 were female and mean age was 45.3 years. A mean duration of uveitis before starting MTX therapy was 1.4 year, ranging from 5 months and 10 years. In most of patients, the duration of MTX therapy was 6 months, except for 1 patient used MTX for 1 year and another patient for 2 years. Mean dose of methotrexate was 5mg per week except that first 2 patients were given 7.5mg/week for the first 4 weeks.

And then the dose was adjusted to 5mg because of drug intolerance associated with severe nausea and mild headache. Mean follow-up was 16.5 months.

Among all patients, anterior uveitis was largest group which accounted for 63.0% (17/27) and then followed by intermediate uveitis (18.5%, 5/27), panuveitis (11.1%, 3/27) and posterior uveitis (7.4%, 2/27). Here, intermediate uveitis included 1 case of pars planitis and 4 cases of anterior and intermediate uveitis in which vitritis was prominent. Etiology of uveitis was shown in table 1.

Table 1. Etiology of uveitis patients

Anatomical Location of Uveitis	Etiology	No. of patients
Anterior	HLA B27+ uveitis	3
	Idiopathic anterior uveitis	14
Intermediate	Pars planitis	1
	Anterior uveitis and intermediate uveitis	4
Panuveitis	VKH syndrome	2
	Behcet's disease	1
Posterior	Multifocal choroiditis	1
	Birdshot retinochoroidopathy	1

Methotrexate showed effectiveness in control of inflammation in 92.6% (25/27) of patients. However, 7.4% (2/27) of patient did not respond to therapy.

Among all patients, 8 were bilateral and 19 were unilateral. Thus, 35 eyes were included in this study. Visual acuity was improved in 29 eyes (82.9%) and in 2 eyes (5.7%) vision was maintained, but 2 patients showed the decreased vision in both eyes (11.4%). This evaluation was based on Log MAR of initial and final visual acuity. 3 patients developed complicated cataract associated with chronic uveitis and were allowed to receive ECCE and IOL implantation to improve visual acuity because inflammation was successfully controlled with MTX. The visual acuity changes of patients are shown in Table 2.

Table 2. Visual acuity changes before and after MTX therapy

	Increase >2 lines	No change	Decrease >2 lines
No. of eyes	29	2	4
Percentage (%)	82.9	5.7	11.4

24 patients (88.9%) had previously taken daily oral prednisolone and 3 were receiving intravenous dexamethasone injection at the time of being offered MTX therapy. Prednisolone was given at a dosage of 30~40mg per day and tapered over several weeks but in most of cases steroid could not be stopped due to flare-ups. After initiating MTX therapy, steroid-sparing effect was achieved in 23 patients (85.2%). 13 patients could stop taking steroid at 6 month of MTX therapy and additionally 10 patients discontinued steroid therapy at the time of 1 year.

The mean number of relapses before starting MTX therapy was 4.2 and it was decreased to 1.9 after medication.

There was no serious side effect requiring discontinuation of medication but mild to moderate adverse reactions were recorded in 22.2% of patients. 2 patients who were given 7.5mg/week of MTX experienced adverse reactions such as severe nausea without vomiting and dizziness or headache that occurred within 4 weeks of initiating therapy. Then dose of MTX was reduced to 5mg/week because of patient's strong complaints of nausea. At dose of 5mg/week, no patient complained of serious nausea or dizziness, but 3 patients experienced mild to moderate fatigue that occurred a few months later. 1 patient developed stomatitis, 1 experienced mild diarrhea and another patient showed mild leukopenia. Adverse effects are listed in Table 3.

Table 3. Adverse effects recorded during MTX therapy

Adverse effects	No. of patients	Percentage (%)
Fatigue	3	11.1
Stomatitis	1	3.7
Diarrhea	1	3.7
Leukopenia	1	3.7

Discussion

Methotrexate is an antimetabolite which has been used to control uveitis from 1960s and its usage in the field of ophthalmology is increasing more and more [8-12]. Reviewing literatures, a lot of ophthalmologists used MTX at various dose ranging from 5 to 40mg per week [8, 13-15]. However, studies which revealed effectiveness of MTX at very low dose of 5mg/week are few.

In this study, 27 patients with chronic noninfectious uveitis were treated with oral MTX at dose of 5mg/week. For the first time, 2 patients were given 7.5mg/week as initial dose of therapy for the first 4 weeks. At first follow-up, these patients strongly complained of adverse effects such as nausea, dizziness and headache. So we adjusted dosage to 5mg/week in order to reduce side effects. Although MTX was given at very low dose, these patients showed satisfactory results both in controlling of uveitis and steroid-sparing effects. Since then, we were very interested in efficacy of MTX at low dose of 5mg/week and investigated it in 27 case series of patients.

In this study, inflammation was controlled in 92.6% of patients at dose of 5mg, once weekly. There are various reports about effects of MTX on inflammation control. Samson et al revealed that intraocular inflammation was controlled with MTX in 76% of patients [8]. Other studies showed that MTX was able to suppress inflammation at the ratio ranging from 45% to 72.6% [17-19]. There are other smaller retrospective studies inflammation reduction was achieved in 60% to 100% of patients [20-23].It is difficult to compare our results with these reports, because this study include small case series, but it showed that 5mg/week MTX was able to sufficiently suppress inflammation in our people.

One of the purposes of using IMT is to reduce prolonged systemic corticosteroids use which frequently results in serious side effects including gastritis, pepticulcer, diabetes, osteoporosis, hypertension, aseptic necrosis of the femoral head, etc. Steroids also affect visual acuity by causing cataracts orglaucoma in uveitic eyes. Many ophthalmologists reported that oral methotrexate showed steroid-sparing effect in

uveitis patients. Samson et al revealed that MTX had steroid-sparing effect in approximately 70% of patients at dose of 7.5~40mg [8]. There are other reports revealed that MTX showed corticosteroid reduction in 50% to 100% of patients [17, 18, 24]. In this study, for 48.2% of patients corticosteroids could be ceased at 6 months of MTX therapy and 37.0% at 1 year of therapy, consequently the discontinuation of steroids was achieved in 85.2%. This result suggested that 5mg per week MTX therapy also had sufficient steroid-sparing effect. We suppose that the main reason to allow discontinuation of steroids was associated with decreased relapse rate.

In this study, except 4 patients, 85.2% of patients showed no relapse from 6 months after MTX therapy and there was no need to continue corticosteroids.

Visual acuity is one of the most important matters for patients and ophthalmologists. When initiating MTX therapy, most of patients included in this study showed poor visual acuity because of severe inflammation or frequent relapse or complications including cataract and floaters. Compared with visual acuity at initiation of therapy, it showed improvement in 29 eyes (82.9%) and there was no significant difference in 2 eyes (5.7%). To be more exact, 3 patients had already developed complicated cataract at the time of initiating therapy and showed no improvement of VA with use of MTX. But 6 months after starting MTX, inflammation was efficiently controlled and showed no relapse, so the patients were allowed to receive ECCE and IOL implantation to finally result in significant improvement of visual outcome. 2 cases whose visual acuity showed no improvement had iridocyclitis with sclerits and idiopathic anterior uveitis, respectively. However, 7.4% of patient included in this study showed decrease in visual outcome. They were diagnosed as Behcet's disease and VKH syndrome.

Generally, MTX is safe medication but still shows serious adverse effects including elevated liver enzymes, leukopenia, nausea, malaise and so on, which sometimes prompt discontinuation of therapy. Samson et al reported that in 18 % of patients had to stop medication because of serious side effects and 43% developed common adverse reactions [8]. In current study, no one developed severe side effect, consequently no one stopped MTX therapy. Only mild to moderate adverse reactions including fatigue, stomatitis, diarrhea and leukopenia were noted in 22.2% of patients.

Declarations

Consent to participate

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

Consent to publish

All participants have consented to the submission of article to the journal.

Funding This study was supported by hospital.

Conflicts of interests The authors declare that they have no conflict of interest.

Compliance with ethical standards

Animal research No animal is included in this study.

Ethical approval All procedures performed were in accordance with the ethical standards of the hospital committee and with the1964 Helsinki declaration and its later amendments or comparable ethical standards.

Availability of data and material All data and material of this manuscript comply with field standards.

Author's contributions

Conceptualization and design: [Yong-Hui Kim], Literature search: [Il-Hyok Kang], Methodology: [Yong-Hui Kim], [Mi-Ryong Ko], Clinical studies:[Yong-Hui Kim], [Mi-Ryong Ko], [Kang-Chol Ryu], [Il-Hyok Kang], Data analysis: [Yong-Hui Kim], [Kang-Chol Ryu], Writing-original draft preparation:[Yong-Hui Kim], [Mi-Ryong Ko], Writing-review and editing:[Mi-Ryong Ko], [Il-Hyok Kang],[Kang-Chol Ryu], Supervision:[Kang-Chol Ryu]

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