Use of methotrexate in patients with uveitis

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ABSTRACT

Methotrexate has been frequently employed to treat ocular inflammatory diseases including uveitis, scleritis, and orbital inflammatory disease. It is effective for intraocular lymphoma when given directly into the eye. No study has assessed its efficacy for eye disease in a randomised, placebo controlled design. This report reviews the literature relevant to methotrexate's utility in the treatment of ocular inflammatory disease.

Introduction

Many structures within the eye or near the eye can be affected by inflammation. Examples include uveitis, conjunctivitis, episcleritis, scleritis, keratitis, optic neuritis, dacroadenitis, orbital myositis, and orbital inflammatory disease. Sometimes ocular inflammation is a manifestation of a systemic disease with inflammation elsewhere in the body; sometimes ocular inflammation occurs without any clinical involvement of other structures. Methotrexate has been tested for many of these entities. And while the proof of its efficacy is rarely based on randomised clinical trials, methotrexate has achieved a niche in the therapeutic armamentarium for eye disease.

Methods

This review is based on a literature search of the National Library of Medicine using keywords such as methotrexate and specific forms of ocular inflammation such as uveitis. In addition, the authors have a combined experience evaluating approximately 3000 patients with uveitis or other forms of vision threatening ocular inflammatory disease.

Uveitis

The uvea is the pigmented and vascular structure between the retina and the sclera. It is derived from neuroectoderm, neural crest cells, and vascular channels. It is divided into the anterior portion, the iris; the middle portion, which is the ciliary body; and the choroid, which extends from the scleral spur anteriorly to the optic nerve posteriorly. Uveitis is a condition involving inflammation of the uveal tract (*i.e.* iris, ciliary body, or choroid) or adjacent ocular structures (*e.g.* retina, optic nerve, vitreous humour, and sclera). So, uveitis is not a single diagnosis but includes a broad spectrum of different diseases, each characterised by intraocular inflammation. Uveitis can be broadly divided into systemic, immune-mediated diseases; masquerade syndromes; infections; and immune-mediated syndromes confined to the eye. Selected examples are given in Table I. Most systemic diseases that affect the uvea do so in a characteristic manner. For example, ankylosing spondylitis usually causes a unilateral, sudden onset, anterior uveitis that usually remits within two months but tends to recur. Behçet's disease causes a recurrent, bilateral, sudden onset uveitis

Table I. Classification of uveitis and representative examples.

Systemic immune-mediated diseases
Ankylosing spondylitis
Behçet's disease
Crohn's disease
Multiple sclerosis
Psoriatic arthritis
Reactive arthritis
Sarcoidosis
Vogt-Koyanagi-Harada syndrome
Immune-mediated syndromes confined to the eye
Birdshot retinochoroidopathy
Multifocal choroiditis
Pars planitis
Serpiginous choroiditis
Sympathetic ophthalmia
Infections
Herpes simplex
Herpes zoster
Syphilis
Tuberculosis
Masquerade syndromes
Lymphoma
Leukemia
Retinal detachment

Table II. Role of methotrexate in uveitis.

Title	First Author	Journal/Year	Main indication	Number of Subjects	Main conclusion
1- Methotrexate for ocular inflammatory diseases (4).	Gangaputra S	*Ophthalmology* 2009	Broad range of ocular inflammatory disorders	384 patients (639 eyes)	- Large retrospective, multicentre study based on SITE database. MTX had consistent steroid sparing effect.
2- Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis (11).	Kaplan-Messas A	*Ocul Immunol Inflamm* 2003	Uveitis and scleritis.	39 patients 36 uveitis 3 scleritis	- 23 of 29 patients who tolerated MTX had complete or partial control of inflammation
3- Methotrexate therapy for chronic non-infectious uveitis: analysis of a case series of 160 patients (5).	Samson CM	*Ophthalmology* 2001	Chronic, non-infectious uveitis	160 patients	- 76% control of inflammation - 56% steroid sparing - 90% acuity same or better
4- Methotrexate treatment for sarcoid-associated panuveitis (12).	Dev S	*Ophthalmology* 1999	Panuveitis in sarcoidosis	11 patients, 20 eyes	- The vast majority of patients benefited and average corticosteroid was reduced from 26.6 mg/day to 1.5 mg/day
5- Long-term follow-up of patients with Birdshot retinochoroidopathy treated with corticosteroid-sparing systemic immunomodulatory therapy (13).	Kiss S	*Ophthalmology* 2005	Long term outcome in Birdshot choroidoretino-pathy. (BSCR)	35 patients	- Retinal function in BSCR was maintained.
6- Low-dose methotrexate therapy for ocular inflammatory disease (14).	Shah SS	*Ophthalmology* 1992	Uveitis (9) Scleritis (4) Orbital disease or myositis (6) Retinal vasculitis (3)	22	- 16 of 22 benefit and 14 of the 16 responders discontinued prednisone
7- Comparison of antimetabolite drugs as corticosteroid-sparing therapy for non-infectious ocular inflammation (15).	Galor A	*Ophthalmology* 2008	90 treated with methotrexate for uveitis or scleritis mainly	total of 257 patients	- Mycophenolate works more quickly in uncontrolled inflammation than MTX
8- Use of methotrexate in the management of sight-threatening uveitis (16).	Bom S	*Ocul Immunol Inflamm* 2001	"Sight-threatening uveitis"	11 patients	- Most patients reduced their corticosteroid requirements and 45% had fewer relapses
9- Low-dose MTX treatment in non-infectious uveitis resistant to corticosteroids (17).	Holz FG	*Ger J Ophthalmol* 1992	To assess the effect of low-dose methotrexate (MTX) in controlling active chronic non-infectious uveitis.	14 patients	- Low-dose MTX therapy may be considered as a therapeutic modality in non-infectious, steroid-refractory uveitis.
10- Combined cyclosporine A-steroid – MTX treatment in endogenous non-infectious uveitis (18).	Pascalis L	*J Autoimmun* 1993	Uveitis resistant to corticosteroids	32 patients	- 20 of 32 patients gained normal vision with an average follow-up of 10 month with a combination that included MTX, cyclosporine, and corticosteroid.
11- Methoitrexate: an option for preventing recurrence of acute anterior uveitis (19).	Munoz-Fernandez S	*Eye* (Lond) 2009	Controlling recurent (>3 times) episodes of acute anterior uveitis in prior year	10 patients one patient refused the treatment	- Decrease in the number of flare-ups from 3.4/year to 0.9/year

that is frequently associated with retinal vasculitis. The pauciarticular, ANA positive subset of patients with juvenile idiopathic arthritis tends to develop an insidious onset, bilateral, anterior uveitis which often does not remit for years.

Traditionally the therapeutic approach to uveitis has differed minimally for different etiologies. For example, most multi-centred clinical trials for uveitis enroll patients with a particular anatomic location for the uveal inflammation but not a specific etiology. To some extent, this approach is changing as the natural history and idiosyncrasies of different forms of uveitis are better appreciated. Behçet's syndrome, for example, is now treated often with infliximab, while our own practice is to use this modality for most other forms of uveitis very sparingly. We recommend intravenous methylprednisolone particularly for children with a diagnosis of Vogt-Koyanagi-Harada syndrome, but

Table III. Role of methotrexate in uveitis that occurs in children especially in association with juvenile idiopathic arthritis.

Title	First Author	Journal/Year	Main indication	Number of Subjects	Main conclusion
12- The use of low dose methotrexate in children with chronic anterior and intermediate uveitis (20).	Malik AR	*Br J Ophthalmol* 2005	Children with chronic uveitis	10 patients	- Visual acuity improved and corticosteroid requirements were reduced.
13- Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis (21).	Foeldvari I	*J Rheumatol* 2005	25 of 38 patients with JIA-associated uveitis received Methotrexate	467 with JIA 38 patients with uveitis	- Many patients had a remission of uveitis on MTX
14- Methotrexate for uveitis associated with juvenile idiopathic arthritis: value & requirement for additional antiinflammatory medication (22).	Heiligenhaus A	*Eur J Ophthalmol* 2007	Chronic iridocyclitis associated with juvenile idiopathic arthritis.	35 consecutive patients with JIA.	- Quiescence of uveitis was obtained in 25 patients. - Additional systemic immunosuppressive drugs were required in another 7 patients.

Table IV. Role of methotrexate in other inflammatory conditions.

Title	First Author	Journal/Year	Main indication	Number of Subjects	Main conclusion
15- Methotrexate therapy for ocular cicatricial pemphigoid (23).	McCluskey P	*Ophthalmology* 2004	Ocular cicatricial pemphigoid.	17 patients	- Low-dose oral MTX monotherapy is found to be beneficial in the treatment of ocular-cicatricial pemphigoid.
16- A role for methotrexate in the management of non-infectious orbital inflammatory disease (24).	Smith JR	*Br J Ophthalmol* 2001	Non-infectious orbital inflammatory diseases	14 patients (24 eyes)	- Effective in controlling non-infectious orbital inflammatory diseases.
17- Use of methotrexate in sarcoid-associated optic neuropathy (25).	Maust HA	*Ophthalmology* 2003	To study possible effect of MTX on sarcoid associated optic neuropathy (SAON).	3 patients with sarcoid associated optic neuropathy.	- All patients had a decrease in their corticosteroid requirements. - All had improved or stabilised visual field.

we rarely use this approach for other forms of uveitis. With the exception of the uveitis in association with juvenile idiopathic arthritis, the published experience in using methotrexate for uveitis is based on series that include diverse forms of uveitis rather than experience with a specific disease entity.

The clinician who is considering the use of an oral immunosuppressive medication to treat uveitis must first exclude either an infection or a malignancy such as a B cell lymphoma. Furthermore, despite their common use, no oral immunosuppressive medication currently is approved by the FDA or comparable regulatory agency to treat uveitis. Some forms of non-infectious uveitis can be managed adequately with only topical corticosteroids or the use of locally injected corticosteroids. Most forms of anterior uveitis respond particularly well to topical corticosteroids, but topical corticosteroids are rarely adequate treatment for inflammation which is posterior to the lens. If local corticosteroids are not adequate, the treating physicians will usually embark on a trial of oral corticosteroids. The early use of corticosteroid-sparing immunosuppression has been advocated by a Delphic panel (1). In many practices, methotrexate is the most popular immunosuppressive for this indication.

In September, 2009, 120 practicing physicians belonging to the American Uveitis Society responded to questions about their practice patterns (N. Acharya, unpublished). Among 7 immunosuppressants, methotrexate was easily the preferred one for treating anterior uveitis. On the other hand, methotrexate ranked second to mycophenolate mofetil as a therapeutic choice to treat intermediate, posterior, or panuveitis. Although many physicians preferred mycophenolate to methotrexate for certain anatomic subsets, methotrexate was still prescribed first for these subsets, about twice as often as mycophenolate. This presumably reflects its lower cost and greater convenience. A dosage of 20mg/week is both the median and mean dosage of methotrexate employed by most uveitis specialists in the American Uveitis Society.

We have compared the persistence of methotrexate in the treatment of uveitis with the persistence of other immunosuppressive medications including azathioprine, cyclosporine, and mycophenolate mofetil (2). Persistence is defined as the length of time that a patient continues to use a medication. Discontinuation of medication is usually due to either intolerance or lack of efficacy.

Table V. Direct intraocular injection of methotrexate.

Title	First Author	Journal/Year	Main indication	Number of Subjects	Main conclusion
18- Intravitreal methotrexate as an adjunctive treatment of intraocular lymphoma (26).	Fishburne BC	*Arch Ophthalmol* 1997	Intraocular lymphoma.	Seven eyes of 4 patients	- Improvement in the survival rates and time to relapse for patients with primary central nervous lymphoma.
19- Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement (27).	Smith JR	*Ophthalmology* 2002	Treatment of intraocular lymphoma	26 eyes in 16 patients	- All patients responded; 3 recurrences responded to repeat treatment.
20- Intraocular methotrexate in ocular diseases other than primary central nervous system lymphoma (28).	Hardwig PW	*Am J Ophthalmol* 2006	Primary CNS lymphoma with ocular involvement.	16 eyes	- Visual acuity improved in 7 eyes and stabilised in 5 eyes.
21- Concurrent administration of intravenous systemic and intravitreal methotrexate for intraocular lymphoma with central nervous system involvement (29).	Nakauchi Y	*Int J Hematol* 2010	Intraocular lymphoma with CNS involvement.	3 eyes of 2 patients	- Concurrent intravenous MTX and intravitreal MTX may be effective for intraocular lymphoma with CNS involvement.
22- Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular oedema (30).	Taylor SR	*Ophthalmology* 2009	Unilateral exacerbation of non-infectious uveitis and/or CME.	Fifteen eyes of 15 patients.	- Improved visual acuity and reduced macular edema but relapse occurs at a median of 4 months.
23- Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience (31).	Frenkel S	*Br J Ophthalmol* 2009	Treatment of intraocular lymphoma.	44 eyes of 26 patients	- Effective control of intraocular lymphoma with intravitreally injected MTX

In our clinics at Oregon Health & Science University, patients continued with methotrexate for roughly twice as long as any of the other agents.

We have summarised the experience in using methotrexate for inflammatory eye diseases in Tables II through V. Table II includes the studies which assessed the effectiveness of methotrexate primarily for uveitis. Table III summarises those studies done specifically in children, usually for uveitis in association with juvenile idiopathic arthritis. Table IV includes studies that dealt with forms of eye inflammation other than uveitis, and Table V notes studies that have been done using an emerging approach, direct intraocular injection of methotrexate.

Several of these studies deserve special comment.

The use of methotrexate in the management of ocular inflammation was first reported in 1965 by Wong and Hersh (3). In this report 9 of 10 patients with a diagnosis of "cyclitis" who were refractory to steroid therapy were deemed to benefit from methotrexate.

The SITE (Study of Immunosuppressive Therapy for Eye Disease) database combines more than two decades of observations from the Wilmer Eye Institute at Johns Hopkins University, the Casey Eye Institute at Oregon Health & Science University, the Massachusetts Eye and Ear Infirmary at Harvard, the University of Pennsylvania, and the National Eye Institute. The SITE study is easily both the largest database and the longest follow-up time for the evaluation of immunosuppression for inflammatory eye disease. It included patients with multiple forms of eye inflammation such as scleritis, mucous membrane pemphigoid (MMP), and orbital inflammatory disease. Combining the data from various practices with different approaches to dosage and administration is no mean feat. The SITE study used a corticosteroid sparing effect as an endpoint that allowed observations from the various practices to be compared. The SITE study included 384 patients (639 eyes) at four tertiary ocular inflammation clinics with uveitis. Complete suppression of inflammation sustained for ≥28 days was achieved by methotrexate within six months in: anterior uveitis (55.6%), intermediate uveitis (47.4%), and posterior or panuveitis (8.6%). A corticosteroid-sparing effect defined as ≤10mg of prednisone per day by six months was achieved in 46.1%, 41.3%, and 20.7%, respectively (4). Methotrexate also had utility for other forms of ocular inflammation.

Samson studied the outcome of 160 patients with chronic non-infectious uveitis who did not respond well to conventional anti-inflammatory therapy and were treated with methorexate. The study showed that inflammation was controlled in 76.2% of the patients

and steroid-sparing effect was achieved in 56% (5).

Comparing the results of these two studies is not practical for many reasons. For instance, in the Samson study methotrexate was not monotherapy in 16 patients where cyclosporine was added to control inflammation, while in the SITE study, methotexate was the only therapy. The definition of a steroid-sparing effect in Samson was ≤8mg, but in the SITE study it was ≤10mg. The definition of being inactive in the Samson study is <1+ cell. In the SITE study it is the absence of cells. While these variables make it very hard to compare the results, both studies conclude that methotrexate is beneficial in the treatment of non-infectious, chronic uveitis. The limitation of both studies is the retrospective design and both studies were conducted in tertiary centres. A strength of both studies is the large sample size. The SITE study suggests that methotrexate had limited efficacy for panuveitis, but it may be that this entity in general is more difficult to control with immunosuppression.

Additional smaller studies on the use of methotrexate for uveitis are summarised in Table II.

Some forms of uveitis are recurrent, such as that associated with ankylosing spondylitis. These recurrences are typically unilateral, anterior, and of limited duration. They are commonly designated as AAU or acute anterior uveitis. A prospective, open-label, longitudinal study included patients from June 2002 to March 2005 who had either three or more episodes of AAU the previous year. This study demonstrated that methotrexate was effective in reducing the mean number of recurrences in the pre-methotrexate year (3.4) (SD 0.52) to 0.89 (SD 1.17) with significant *p*-value (p=0.011). Other medications including non-steroidal anti-inflammatory drugs, sulfasalazine, and TNF inhibitors have also been reportedly effective in reducing the frequency of recurrent AAU and in controlling other associated manifestations such as hip and back involvement in ankylosing spondylitis (6-10).

As shown in Table III, methotrexate has also proven very popular in the treatment of children who suffer from the chronic, anterior, bilateral uveitis that occurs commonly in association with the pauciarticular subset of patients with juvenile idiopathic arthritis. For example, in 2006, a large prospective study was conducted in Hamburg, Germany, which included a retrospective chart review of patients with a diagnosis of JRA; it included 467 patients; 35 patients were diagnosed with uveitis, 31 with oligoarticular arthritis, and seven psoriatic arthritis. Out of 35 patients 25 were treated with a low dose of methotrexate at a mean dose of 15.6mg/month. Remission occurred after 4.25 months (1-12). The mean duration of the remission was 10.3 months (3-27). Overall, the total duration of methotrexate therapy was 661 months and patients were in remission for 417/661 months. If systemic immunosuppression is deemed appropriate for a child with uveitis, methotrexate is usually the first choice for multiple reasons which include efficacy, convenience, cost, tolerability, and experience.

As noted in Table IV, methotrexate has also been used for a diverse array of other inflammations in and around the eye. These conditions include scleritis, mucous membrane pemphigoid, orbital inflammatory disease, and the optic neuropathy which can be associated with sarcoidosis.

A more recent approach to methotrexate therapy for uveitis has been treatment based on intravitreal injection. It is unclear how much of the efficacy of methotrexate is based on levels achieved locally within the eye, but levels of methotrexate have been detected in the eye after systemic administration. The first studies on intravitreal methotrexate (Table V) were for the treatment of intraocular lymphoma. A B cell lymphoma usually in association with primary central nervous system lymphoma is a rare but a clinically extremely important uveitis masquerade syndrome. This malignancy within the eye responds very well to methotrexate injected into the eye. Traditionally there has been a great deal of reluctance to inject into the eye because of concerns about cataract, infection, retinal detachment or bleeding. The current treatment for the neovascular complication of macular degeneration, however, requires recurrent intravitreal injections of antibodies to vascular endothelial growth factor. This practice norm has made many ophthalmologists comfortable with the intravitreal delivery of medication. Intravitreal methotrexate is still not an accepted standard of care, but it can be considered in a patient who needs sustained delivery of treatment and who has a history of poor compliance with medications, in a patient with primarily unilateral, intermediate or posterior disease, or in a patient who is intolerant of oral or local corticosteroids. In addition to the risk of the injection itself, the most common adverse effect from intravitreal methotrexate injection is toxicity to the corneal epithelium. This is usually transient and can be treated with topical folinic acid.

Although there is a relatively large body of data to support the use of methotrexate for ocular inflammatory diseases, there are no large, prospective, randomised controlled trials. Our own approach to treating patients with non-infectious forms of uveitis is usually to try to control the inflammation with local corticosteroids. If this fails, we most often resort to oral corticosteroids, but we will opt for a steroid sparing drug if the patient experiences steroid related side effects or cannot taper below 10mg/day of prednisone. Methotrexate is usually our first choice for a steroid sparing drug unless there is an apparent contraindication such as a history of liver disease, heavy alcohol use, or a prior history of viral hepatitis. We usually strive to achieve a dose of around 20mg/week if the patient tolerates this and we prefer subcutaneous injection to oral dosage if accepted by the patient. We administer the methotrexate with daily folic acid. Based on the data reviewed above and the survey of members of the American Uveitis Society, methotrexate has found a valuable niche in the therapy of uveitis.

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