Intraocular Methotrexate in the Treatment of Uveitis and Uveitic Cystoid Macular Edema

Simon R. J. Taylor, MA, FRCOphth,[1] *Zohar Habot-Wilner, MD,*[1] *Patricio Pacheco, MD,*[2] *Sue L. Lightman, PhD, FRCOphth*[1]

Objective: A pilot study to evaluate the use of intravitreal methotrexate (MTX) for the treatment of uveitis and uveitic cystoid macular edema (CME).

Design: Prospective, consecutive, interventional case series.

Participants: Fifteen eyes of 15 patients with a unilateral exacerbation of noninfectious intermediate, posterior uveitis, or panuveitis and/or CME such that visual acuity (VA) was 20/40 or worse, together with a history of increased intraocular pressure (IOP) in response to corticosteroid administration.

Intervention: Intravitreal injection of 400 μg in 0.1 ml MTX.

Main Outcome Measures: The primary outcome measure was VA (using the Early Treatment Diabetic Retinopathy Study chart). Other outcome measures included ocular inflammation scores, time to relapse, levels of systemic corticosteroid and immunosuppressive therapy, and ocular coherence tomography. Potential complications of intravitreal MTX injection, including cataract progression, vitreous hemorrhage, retinal detachment, and corneal epitheliopathy, were assessed.

Results: VA improved at all time points and was statistically significant at the 3- and 6-month follow-up examinations. The mean visual improvement was 4 lines at 3 months and 4.5 lines at 6 months, with no statistical difference between the best VA obtained after MTX injection and after previous corticosteroid treatment, including intravitreal triamcinolone acetate injection. Five patients relapsed after a median of 4 months; a similar improvement was seen after re-injection. Ocular inflammation scores improved at all time points, and systemic immunosuppressive medication was reduced in 3 of 7 patients taking this at the start of the trial.

Conclusions: In patients with uveitis and uveitic CME, intravitreal MTX can improve VA and reduce CME and, in some patients, allows the reduction of immunosuppressive therapy. Relapse occurs at a median of 4 months in some patients, but reinjection has similar efficacy.

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Uveitis and its sight-threatening sequelae, such as cystoid macular edema (CME), may be treated locally with periocular or intravitreal injections of corticosteroids or systemically with oral corticosteroids or other immunosuppressive drugs. Local treatment is preferred where possible, especially for unilateral disease. However, local administration of corticosteroids is associated with an increase in intraocular pressure (IOP) in some patients, which can limit their treatment options still further. An alternative agent would prove extremely useful in such cases.

Methotrexate (MTX) has been used increasingly in ophthalmic disease, both locally and systemically. Various ophthalmic inflammatory conditions are indications for systemic therapy,[1] and intraocular lymphomas associated with primary central nervous system lymphoma have been successfully treated with intravitreal injections of MTX.[2,3]

Hardwig et al[4] recently reported a retrospective small case series in which patients were treated with 400 μg intraocular MTX for ocular disease other than primary central nervous system lymphoma. The majority of patients had either uveitis or advanced proliferative diabetic retinopathy, and they reported retention or improvement of visual acuity (VA) in 75% of patients, with complications consisting of 1 case of corticosteroid-responsive sterile endophthalmitis among the 16 eyes studied. The 4 eyes with intraocular inflammation or CME all responded well to 400 μg intravitreal MTX. Thus, on this limited evidence, a dose of 400 μg seems to be well tolerated and to have some efficacy.

The aim of this pilot study was to examine whether intravitreal MTX provides an alternative for intraocular steroid therapy in patients with unilateral intermediate or posterior uveitis and/or CME who are also known steroid responders.

Patients and Methods

This study was a prospective, interventional, consecutive case series of patients with unilateral reactivation of noninfectious intermediate, posterior uveitis, or panuveitis and/or CME. The study included 15 patients, 15 eyes, and 19 injections. MTX is not licensed in the United Kingdom for intravitreal use, but approval for this prospective study was gained from the local ethics committee and the UK Medicines and Healthcare products Regulatory Agency. Informed consent was obtained from all patients.

Seven patients were female, and 8 patients were male. The median age was 50 years (range, 25–68 years, Table 1). Inclusion

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Table 1. Baseline Characteristics of the Patient Cohort

Study Eye	Age (y)	Sex	Diagnosis	Vitreous Haze	CME, Duration	Previous IVTA	Previous Surgery	Systemic Therapy Failed at Time of MTX Injection
1	68	F	CAU+CME	—	Y, 40 mo	N	Cataract	Nil
2	55	F	CAU+CME	—	Y, 54 mo	Y	PPV, ERM peel, cataract	Nil
3	50	F	CAU+CME	—	Y, 18 mo	N	PPV for MH, cataract	Nil
4	65	M	CAU+CME	—	Y, 6 mo	N	Cataract	Nil
5	43	M	Intermediate	+	Y, 2 mo	Y	Nil	Prednisolone
6	46	M	Intermediate	++	Y, 6 mo	N	Nil	Nil
7	30	M	Intermediate	++	Y, 2 mo	N	Cataract	Prednisolone, mycophenolate mofetil
8	54	M	Intermediate	++	Y, 3 mo	N	Nil	Nil
9	37	F	Intermediate	++	Y, 1 mo	N	Nil	Prednisolone
10	58	M	Intermediate	+	Y, 3 mo	N	Cataract, MMC trabeculectomy	Prednisolone
11	25	M	Intermediate	+++	Y, 48 mo	N	Cataract	Prednisolone
12	26	F	Intermediate	—	Y, 3 mo	Y	Nil	Prednisolone
13	60	M	Panuveitis	++	Y, 3 mo	Y	Cataract	Nil
14	63	F	Panuveitis	+	Y, 18 mo	N	PPV, cataract	Prednisolone
15	45	F	Panuveitis	++	Y, 54 mo	N	Cataract, MMC trabeculectomy	Nil

Cataract = phacoemulsification of lens with intraocular lens implant; CAU = chronic anterior uveitis; CME = cystoid macular edema; ERM = epiretinal membrane; IVTA = intravitreal injection of 4 mg triamcinolone acetate; MH = macular hole; MMC = mitomycin C; MTX = methotrexate; PPV = pars plana vitrectomy.
Duration of CME refers to current episode.

criteria included a diagnosis of unilaterally active, noninfectious, intermediate, posterior uveitis, or panuveitis and/or CME such that VA was reduced to the equivalent of 20/40 or worse. All patients also had a history of increased IOP in response to corticosteroid administration. In line with the summary of product characteristics of MTX, pregnant or lactating women were excluded and contraceptive advice was given to women and men with partners of childbearing age. Seven of 15 patients were taking corticosteroid and/or immunosuppressive medication at enrollment. The doses of any systemic medication were stable for at least 2 months before study enrollment and were not altered on entry into the trial.

Median best-corrected baseline VA was 20/200 (range, 20/40 to counting fingers at 2 feet) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Four of the patients had anterior uveitis with long-standing CME of at least 6 months' duration, 8 patients had intermediate uveitis with active vitritis and CME, and 3 patients had panuveitis with vitritis and CME. The median duration of CME during the current episode of disease activity was 6 months (range, 1–54 months). Three of the patients were previously vitrectomized, and 10 patients had undergone cataract surgery with posterior chamber lens implantation. Four patients had previously undergone an intravitreal injection of 4 mg triamcinolone acetate (IVTA).

Intravitreal MTX injections were performed aseptically after the topical application of anaesthesia and 5% povidone iodine to the conjunctival sac. Each patient received an intravitreal injection of 400 μg of MTX in 0.1 ml, 3.5 to 4.0 mm posterior to the inferotemporal limbus, depending on lens status, with a 27-gauge needle.

Patients were examined at 1 week postinjection and monthly thereafter for a period of 6 months. Best-corrected ETDRS vision, slit-lamp examination, and dilated fundus examination were performed. Ocular inflammation was graded according to the Standardization of Uveitis Nomenclature working group recommendations.[5] Optical coherence tomography (OCT) was performed, where possible, every 2 months, using a high-resolution Stratus 3000 OCT model (Carl Zeiss Meditec Inc., Dublin, CA) with software version 4.0 to measure macular thickness. Macular thickness was defined as the distance between the internal retinal border (inner nerve fiber layer border) and external retinal border (retinal pigment epithelium/outer segment photoreceptor hyperreflective layer) and was performed manually.

Changes from baseline VA, ocular inflammation scores, and OCT volume and thickness were compared at each visit. Where ocular inflammation and/or CME improved and patients were taking oral corticosteroids (often with additional immunosuppressive agents), the dose per day was gradually tapered at the 2-month visit. Likewise, the dose of second-line immunosuppressive agents, when patients were taking them, was reduced. MTX injections were not repeated within a 3-month window, but if inflammation or CME subsequently recurred, then patients were offered a repeat intravitreal injection. If patients developed bilateral inflammation, standard oral corticosteroid therapy was begun and they were not offered further MTX injections within the study.

Data Analysis

Response to treatment was defined as a gain of at least 10 ETDRS letters in association with a decrease in posterior uveitis and/or CME. Relapse was defined as a loss of greater than 5 letters from the best postinjection VA associated with the recurrence of posterior uveitis and/or CME.

Means and standard errors (SEs) were obtained for the logarithm of the minimum angle of resolution (logMAR) before injection and at 1 week and 1 to 6 months after injection and for the macular thickness at 2, 4, and 6 months after injection. *P* values were calculated using Wilcoxon matched pair *t* tests. GraphPad Prism v5.01 software (GraphPad Software Inc., San Diego, CA) was used for all analyses. The accepted level of significance for all tests was $\alpha = 0.05$.

Results

Twelve of the 15 patients were followed up for 6 months after their first injection. Patient 8 left the study in week 8, having been placed on 40 mg prednisolone as CME prophylaxis for other eye cataract surgery. He had not responded to intravitreal MTX in his study eye (logMAR 1.54 at baseline and 1.48 at week 4), but VA responded rapidly to oral prednisolone over the following 4 weeks

(logMAR 0.40). Patient 12 left the study after the week 12 visit after developing bilateral intermediate uveitis with CME. Patient 11 left the study at week 16 after developing a dense posterior capsular plaque that needed vitrectomy and surgical capsulotomy.

Effects of Intravitreal Methotrexate on Uveitis and Uveitic Cystoid Macular Edema

VA results were expressed in logMAR. MTX injections proved effective at improving VA over the course of the follow-up period. Sixty-seven percent of patients (10/15) had a response to treatment as defined by a gain of at least 10 letters (i.e., 2 lines) by 1 month and 87% (13/15) by 3 months (Fig 1). Five patients achieved a VA of better than 20/40 in response to MTX injection. Mean preinjection vision was 1.06 (SE, ±0.12, n = 15, ≈20/200). Mean postinjection vision was 0.82 (SE, ±0.13, n = 15, ≈20/120) at 1 week, 0.73 (SE, ±0.12, n = 15, ≈20/100) at 1 month, 0.63 (SE, ±0.11, n = 14, ≈20/80) at 3 months, and 0.59 (SE, ± 0.09, n = 12, ≈20/80) at 6 months.

Vitreous haze scores also improved over the course of the study. The mean baseline vitreous haze score was 1.40 (SE, ±0.16, n = 15) and improved to 0.70 (SE, ±0.23, n = 15, $P = 0.07$) at 1 month, 0.50 (SE, ±0.17, n = 14, $P<0.05$) at 3 months, and 0.25 (SE, ±0.18, n = 12, $P<0.01$) at 6 months.

Macular thickness also improved after MTX injection. Optical coherence tomography examinations were attempted in all patients and obtained for 10 of the 15 patients; in 5 patients, media opacities precluded reliable examination. The mean baseline macular thickness was 425 μm (SE, ±57 μm, n = 10). This decreased to 299 μm (SE, ±55 μm, n = 10, $P<0.01$) at 2 months, 291 μm (SE, ±53 μm, n = 10, $P<0.01$) at 4 months, and 275 μm (SE, ±51 μm, n = 10, $P<0.01$) at 6 months. Data for VA and macular thickness at each time point are included in Table 2.

Seven patients were on systemic therapy for the study eye at enrollment in the trial. In 3 of these, it proved possible to reduce their immunosuppressive medication over the course of the period of follow-up. Patient 14 was taking 5 mg prednisolone at the start of the trial, and this was reduced to 2 mg by month 6. Patient 5 was taking 10 mg prednisolone at the start of the trial, and this was reduced to 2.5 mg by month 6. Patient 7 was taking 15 mg prednisolone at the start of the trial, and this was reduced to 10 mg by month 4.

Table 2. Logarithm of the Minimum Angle of Resolution, Visual Acuity, and Optical Coherence Tomography Measurements of Macular Thickness

Visit	LogMAR (SE)	Macular Thickness/μm (SE)
Baseline	1.06 (0.12) (n = 15)	425 (57) (n = 10)
1 wk	0.76 (0.12) (n = 14, $P<0.01$)	
1 mo	0.73 (0.12) (n = 15, $P<0.01$)	
2 mo	0.67 (0.11) (n = 14, $P<0.01$)	299 (55) (n = 10, $P<0.01$)
3 mo	0.63 (0.11) (n = 14, $P<0.01$)	
4 mo	0.77 (0.13) (n = 13, $P<0.01$)	291 (53) (n = 10, $P<0.01$)
5 mo	0.64 (0.10) (n = 12, $P<0.01$)	
6 mo	0.59 (0.09) (n = 12, $P<0.01$)	275 (51) (n = 10, $P<0.01$)

LogMAR = logarithm of the minimum angle of resolution; SE = standard error.
P values are Wilcoxon matched-pair *t* tests, each compared with baseline.

Comparison of the Results of Intravitreal Methotrexate Injection with Potential Best Visual Acuity

To estimate the efficacy of intravitreal MTX injection, we ascertained each patient's potential best VA. This was determined as the best VA recorded within the 12 months before study enrollment; in 11 patients this was while they were receiving high-dose corticosteroids, and in 4 patients this was after IVTA injection. This was then plotted against the best recorded VA after intravitreal MTX injection (Fig 2). There was no significant difference between the potential best VA and the best VA achieved after intravitreal MTX injection.

Duration of Effect and Repeat Injections

We next looked at the duration of effect of a single intravitreal injection of MTX. Relapse was defined as a loss of at least 5 letters (i.e., 1 line) from the best VA recorded postintravitreal MTX injection, associated with the recurrence of posterior uveitis and/or CME. Of the 13 patients who responded to MTX injections, 5 relapsed according to this definition. The median time to relapse was 4.0 months (range, 1–4 months) and is illustrated by the

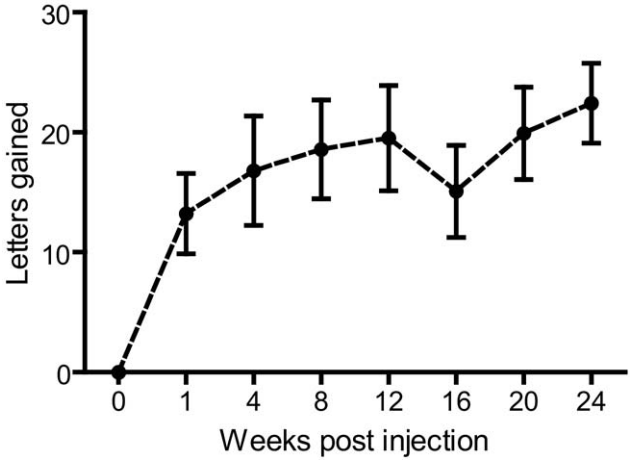

Figure 1. Number of letters gained, mean ± standard error (SE) of the mean. The decline in acuity between weeks 12 and 16 is due to disease relapse in 5 of the 15 patients; the subsequent improvement at weeks 20 and 24 is due to the effect of repeated injection of methotrexate (MTX).

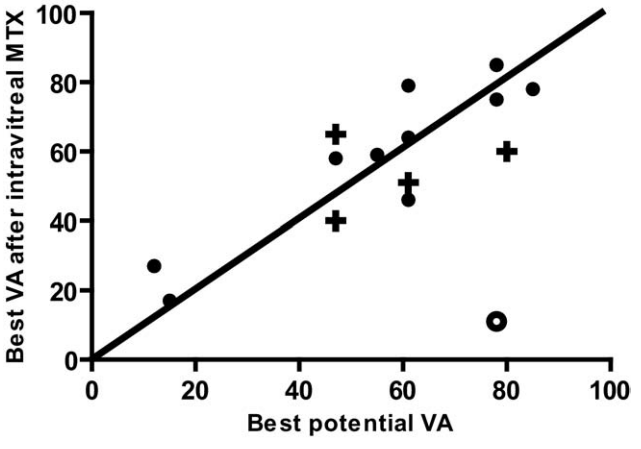

Figure 2. Comparison of VA obtained after intravitreal MTX compared with estimated potential best VA on systemic corticosteroids and immunosuppressive agents (*circles*) or after IVTA (*crosses*). The outlier (*open circle*) represents patient 8, who left the trial at week 8. MTX = methotrexate; VA = visual acuity.

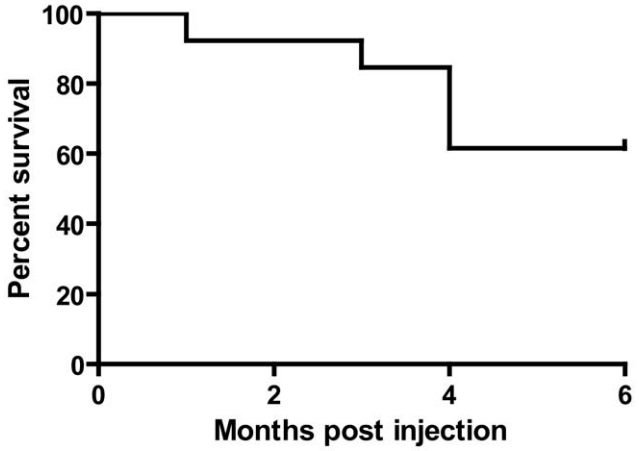

Figure 3. Kaplan–Meier curve showing time to relapse for the 13 patients who responded to intravitreal methotrexate (MTX) injection.

decline in mean VA between 12 and 16 weeks (Fig 1). Patient 1 was not classed as a relapse despite a loss of 8 letters at month 2 because this was due to the development of temporary corneal epitheliopathy rather than active inflammation or CME, and VA subsequently recovered without further intervention (Fig 3).

Four patients had repeat injections after relapse (patients 2, 3, 7, and 13). Each patient improved once again after treatment, gaining a median of 17 letters (range, 6–23 letters) by month 2 after reinjection.

Side Effects of Intravitreal Methotrexate

There were no injection-related adverse events other than mild ocular pain for less than 24 hours' duration. No patients had increased IOP after MTX injection. Patient 1, who was pseudophakic, developed corneal epitheliopathy 2 months after her initial injection. This was treated symptomatically and resolved by month 6. Patient 11, who was also pseudophakic, developed dense posterior capsular opacification by week 16, which was felt unlikely to be due to MTX administration. No other drug-related adverse events were recorded.

Discussion

This prospective study demonstrates the effects of intravitreal MTX in patients with uveitis and uveitic CME. Although it is a noncomparative case series, the results suggest that intravitreal MTX is an effective treatment for uveitis and uveitic CME, expanding on the results of a previous small study.[4]

Local treatment of uveitis is preferred where possible, especially for unilateral disease, because it avoids the potential side effects of systemic corticosteroids and immunosuppressive agents. Periocular corticosteroids are useful for mild to moderate inflammation,[6] and IVTA is useful for more severe disease.[7] Indeed, corticosteroids constitute the only intraocular medications that are currently used to treat refractory CME from noninfectious uveitis.[8–11] However, all forms of corticosteroids can increase IOP, and more than 40% of patients have a significant increase in IOP after IVTA.[7,12] In steroid responders, patients who are already known to develop increased IOP in response to corticosteroid administration, an alternative agent that could be administered locally would therefore be of use.

Methotrexate is a competitive inhibitor of dihydrofolate reductase, and systemic MTX has been used as a steroid-sparing agent for the treatment of noninfectious uveitis for many years.[1,13,14] Intravitreal MTX has been widely used to treat ocular lymphoma that is refractory to systemic chemotherapy and radiation,[15] and a dose of 400 μg is clinically well tolerated.[2,3] Rabbit studies have shown that this dose is nontoxic by electroretinogram study and remains at therapeutic levels for 48 hours.[16] One group performed a rabbit study that suggested that intravitreal MTX reduces the risk of development of endophthalmitis[17] and that this may render it a safer option for the local treatment of refractory uveitis than intravitreal steroids. MTX has not been reported to induce ocular hypertension, a frequent complication of IVTA.[7,12,18]

Thirteen of the 15 patients enrolled in this trial responded to intravitreal MTX injections with an increase in VA associated with decreased intraocular inflammation and macular thickness. This response was rapid, with a significant increase in VA and decrease in ocular inflammation and CME within 1 week. The 2 patients who failed to respond according to the criteria of the trial both had intermediate uveitis. The first withdrew from the study when he commenced 40 mg prednisolone as prophylaxis for cataract surgery in the non-study eye 7 weeks after MTX injection. His VA had only improved by 0.06 logMAR by this stage, but markedly improved with systemic steroid therapy. The second patient improved by 0.12 logMAR over 2 months before developing bilateral disease that necessitated systemic corticosteroids.

Several of the patients also had marked macular scarring or had previously had epiretinal membranes or macular holes, all of which can reduce potential VA. We therefore established a best potential VA for each patient to determine how effective MTX was. The results of intravitreal MTX injection were not significantly different in the best potential VA for each patient. The side effect profile of intravitreal MTX treatment also proved acceptable in our study. One patient developed transient corneal epitheliopathy, and 1 pseudophakic patient developed dense posterior capsular opacification, and 1 other pseudophakic recorded drug-related adverse events. The response to treatment was rapid, with 10 of 15 patients gaining 2 lines within 1 week of intravitreal MTX injection. This may represent the known anti-inflammatory actions of MTX on neuropeptides[19,20] rather than its immunosuppressive effects.

Of the 13 patients in our study who responded to intravitreal MTX, 5 subsequently relapsed. Two of these patients had chronic anterior uveitis with CME, 2 patients had intermediate uveitis, and 1 patient had panuveitis. The median time to relapse was 4 months in these patients. Four elected to undergo a further injection of MTX, to which all 4 patients responded once again.

This cohort is representative of a group of patients who are difficult to treat and present a considerable therapeutic dilemma. The well-established side effects of systemic corticosteroid and immunosuppressive therapy are harder to justify for unilateral ocular disease, and being a steroid

responder increases the risk profile of local corticosteroid therapy. These patients are therefore often undertreated for their ocular disease, and as a consequence have less well-controlled ocular inflammation and CME. Chronic CME is known to lead to ultrastructural changes in both the retina and the retinal pigment epithelium, some of which can be observed clinically,[21–23] and is associated with impaired VA.[24,25] An alternative agent to IVTA that can be administered as local therapy and that is not associated with an increase in IOP would therefore be of considerable use in these patients. We conclude from our pilot study that intravitreal MTX injection may provide such an alternative local therapy for uveitis and uveitic CME and merits further study.

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[1] Department of Clinical Ophthalmology, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London, United Kingdom.

[2] Moorfields Eye Hospital, London, United Kingdom.

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Correspondence:
Sue Lightman, PhD, FRCOphth, Department of Clinical Ophthalmology, UCL Institute of Ophthalmology, Moorfields Eye Hospital, London EC1V 2PD. E-mail: s.lightman@ucl.ac.uk.