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Outcome of Intravitreal Methotrexate in the Treatment of Uveitis and Uveitic Cystoid Macular Edema: A Case Series from a Tertiary Care Hospital in Lahore

Dr. Muhammad Hassan Aftab[1]*, Dr. Mohammad Ahmed Imran[1], Dr. Muhammad Nauraiz Zubair Chawla[2], Dr. Muhammad Hamza Tariq[3], Dr. Bushra Nawaz[4]

[1]Registrar, Eye unit 2, Jinnah Hospital/Allama Iqbal Medical College, Lahore.
[2]Postgraduate Resident, Eye Deptt, Sahiwal Teaching Hospital, Sahiwal.
[3]Postgraduate Resident, Ali Trust Free Eye Hospital Okara
[4]Postgraduate Resident, Eye Deptt, Faisal Masood Teaching Hospital, Sargodha

***Corresponding Author:** Dr. Muhammad Hassan Aftab, Registrar, Eye unit 2, Jinnah Hospital/Allama Iqbal Medical College, Lahore.
Email: mhassan.aftab4@gmail.com

CONFLICT OF INTEREST
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ABSTRACT

Background: Uveitis is an important cause of preventable visual morbidity. In non-infectious disease, corticosteroids and systemic immunomodulatory therapy remain central to management, but treatment-related toxicity and the need for targeted ocular therapy have encouraged interest in local drug delivery. Intravitreal methotrexate has been used as a local anti-inflammatory treatment for selected cases of uveitis and uveitic cystoid macular edema (CME), although contemporary evidence remains limited and heterogeneous.

Objective: To determine the outcome of intravitreal methotrexate in the treatment of uveitis and uveitic cystoid macular edema.

Methods: This single-centre interventional case series was conducted at the Department of Ophthalmology, Jinnah Hospital, Lahore, from 2 January to 1 July 2023. Sixty-five eyes of 65 patients aged 40–70 years with uveitis or uveitic CME were enrolled by non-probability consecutive sampling. Each study eye received a single intravitreal injection of methotrexate 400 µg/0.1 mL. Best-corrected visual acuity (BCVA; Snellen decimal notation) and central macular thickness (CMT; optical coherence tomography) were assessed at baseline and 12 weeks. Baseline and 12-week measurements were compared as paired observations; subgroup comparisons of 12-week outcomes were exploratory. A p-value <0.05 was considered statistically significant.

Results: Mean age was 55.20 ± 6.02 years; 36 patients (55.38%) were male. Mean BCVA increased from 0.30 ± 0.03 at baseline to 0.59 ± 0.04 at 12 weeks (mean change +0.29; p<0.001), while mean CMT decreased from 407.34 ± 27.74 µm to 263.05 ± 12.19 µm (mean change −144.29 µm; p<0.001). Exploratory subgroup analysis showed higher 12-week BCVA in patients aged 56–70 years, those with symptom duration >6 months, and those without diabetes mellitus. Daily computer use >6 hours was associated with lower 12-week CMT. Other subgroup comparisons were not statistically significant.

Conclusion: In this case series, a single intravitreal methotrexate injection was associated with substantial short-term improvement in BCVA and reduction in CMT at 12 weeks. Because the study was uncontrolled and subgroup analyses were exploratory, comparative effectiveness, durability, safety, and treatment-effect modifiers require confirmation in controlled studies.

Keywords	Uveitis; Methotrexate; Cystoid macular edema; Best-corrected visual acuity; Intravitreal injection.
Acknowledgement	The authors acknowledge the patients who participated in this study.
Aftab MH et al. Short Title	Intravitreal Methotrexate for Uveitis and Uveitic CME

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INTRODUCTION

Uveitis comprises a heterogeneous group of inflammatory disorders involving the uveal tract and, frequently, adjacent ocular structures. Non-infectious uveitis is an important cause of visual impairment and affects individuals across the adult age range, with substantial variation in incidence, prevalence, anatomical distribution, and associated systemic disease. Contemporary Standardization of Uveitis Nomenclature (SUN) work has strengthened the classification framework used in clinical research and emphasizes accurate characterization of uveitic entities (1-3). Macular edema is a major sight-threatening complication of intermediate, posterior, and panuveitis. Corticosteroids remain a mainstay of therapy, while conventional immunosuppressive and biologic agents are used when prolonged control or steroid-sparing systemic treatment is required. Local intraocular treatment can deliver high drug concentrations to the eye while limiting systemic exposure, and current local options include corticosteroids, anti-vascular endothelial growth factor agents, and selected immunomodulatory drugs (4-7).

Methotrexate is an antimetabolite with immunomodulatory effects and has been used systemically in non-infectious uveitis as well as intravitreally for selected ocular inflammatory conditions. Evidence for intravitreal methotrexate in uveitic macular edema includes earlier interventional series and, more recently, randomized comparative data and systematic review evidence. The 2023 MERIT trial demonstrated anatomical improvement with intravitreal methotrexate at 12 weeks, although dexamethasone implant produced a larger reduction in macular edema in that trial (8,9). Data from South Asian clinical settings remain limited, and treatment response may vary according to case mix, inflammatory activity, comorbidity, and previous or concomitant therapy. This study therefore evaluated the 12-week visual and anatomical outcomes after a single intravitreal methotrexate injection in patients with uveitis and uveitic CME treated at a tertiary-care hospital in Lahore.

MATERIALS AND METHODS

Study Design, Setting and Duration

This single-centre interventional case series was conducted in the Department of Ophthalmology, Jinnah Hospital, Lahore, from 2 January 2023 to 1 July 2023. Outcomes were assessed 12 weeks after intravitreal treatment.

Sample Size and Sampling Technique

The required sample was 65 eyes. The calculation used a 95% confidence level, an anticipated standard deviation of 0.41 for BCVA from previously reported intravitreal methotrexate data, and an absolute precision of 0.10: $n = (Z\alpha/2 \times SD / d)^2 = (1.96 \times 0.41 / 0.10)^2 = 64.6$, rounded to 65. Patients were enrolled from the outpatient department by non-probability consecutive sampling.

Participants and Eligibility Criteria

Patients aged 40–70 years of either gender with uveitis or uveitic cystoid macular edema were eligible. Exclusion criteria were previous methotrexate exposure, known allergy to methotrexate, previous ocular surgery or trauma, or severe active ocular infection on clinical examination. One eye per patient was included, yielding 65 eyes from 65 patients.

Operational Definitions and Outcome Measures

For study eligibility, uveitis was operationally defined as intraocular inflammation with anterior chamber flare >+1 and anterior chamber cells >+1 on clinical examination. Uveitic cystoid macular edema was defined as intraocular inflammation with blurred vision and central macular thickness >350 µm on optical coherence tomography (OCT). The principal 12-week outcomes were best-corrected visual acuity (BCVA), measured with a Snellen chart and expressed in decimal notation, and central macular thickness measured by OCT. These measures represent complementary functional and anatomical outcomes commonly used in studies of uveitic macular edema (8-10).

Procedure

After written informed consent, demographic and clinical variables were recorded on a structured proforma, including age, gender, duration of symptoms, contact lens use, spectacle use, daily computer use >6 hours, smoking status, diabetes mellitus, hypertension, chronic headache, laterality, and underlying disease. Baseline BCVA and central macular thickness were documented before treatment. Each study eye received a single intravitreal injection of methotrexate 400 µg in 0.1 mL, administered 3.5–4.0 mm posterior to the inferotemporal limbus according to lens status using a 27-gauge needle. BCVA and central macular thickness were reassessed at 12 weeks using the same clinical methods.

Statistical Analysis

Data were analysed using SPSS version 26.0. Quantitative variables were summarized as mean ± standard deviation (SD), and categorical variables as frequency and percentage. Because baseline and 12-week measurements were obtained from the same study

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eyes, within-eye changes in BCVA and CMT were analysed as paired observations using a paired-samples t-test. Mean change was calculated as the 12-week value minus the baseline value. Exploratory subgroup comparisons of 12-week BCVA and CMT across binary baseline characteristics were performed with independent-samples t-tests. These subgroup analyses were interpreted as associations with the 12-week outcome rather than proof of differential treatment response. A two-sided p-value <0.05 was considered statistically significant. Written informed consent was obtained from participants before study-related data collection and intravitreal treatment.

RESULTS

Sixty-five eyes of 65 patients were included. Age ranged from 40 to 70 years, with a mean of 55.20 ± 6.02 years. Thirty-eight patients (58.46%) were aged 40–55 years and 27 (41.54%) were aged 56–70 years. Thirty-six patients (55.38%) were male and 29 (44.62%) were female. Mean symptom duration was 6.66 ± 2.31 months. Baseline demographic and clinical characteristics are shown in Table 1.

Table 1. Baseline demographic and clinical characteristics (n = 65).

Characteristic	Category	n (of 65)	%
Age group	40–55 years	38	58.46
	56–70 years	27	41.54
Gender	Male	36	55.38
	Female	29	44.62
Duration of symptoms	≤6 months	30	46.15
	>6 months	35	53.85
Diabetes mellitus	Yes	27	41.54
	No	38	58.46
Hypertension	Yes	21	32.31
	No	44	67.69
Smoking	Yes	10	15.38
	No	55	84.62
Chronic headache	Yes	10	15.38
	No	55	84.62
Contact lens use	Yes	15	23.08
	No	50	76.92
Glasses use	Yes	19	29.23
	No	46	70.77
>6 hours computer use daily	Yes	12	18.46
	No	53	81.54

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At 12 weeks, mean BCVA increased from 0.30 ± 0.03 to 0.59 ± 0.04, corresponding to an absolute mean increase of 0.29 in decimal acuity ($p<0.001$). Mean CMT decreased from 407.34 ± 27.74 µm to 263.05 ± 12.19 µm, an absolute mean reduction of 144.29 µm (approximately 35.4% of the baseline mean; $p<0.001$). These primary outcomes are summarized in Table 2 and Figures 1 and 2.

Table 2. BCVA and central macular thickness before and 12 weeks after intravitreal methotrexate.

Parameter	Baseline	12 weeks	Mean change	p-value
BCVA (decimal)	0.30 ± 0.03	0.59 ± 0.04	+0.29	<0.001
Central macular thickness (µm)	407.34 ± 27.74	263.05 ± 12.19	−144.29	<0.001

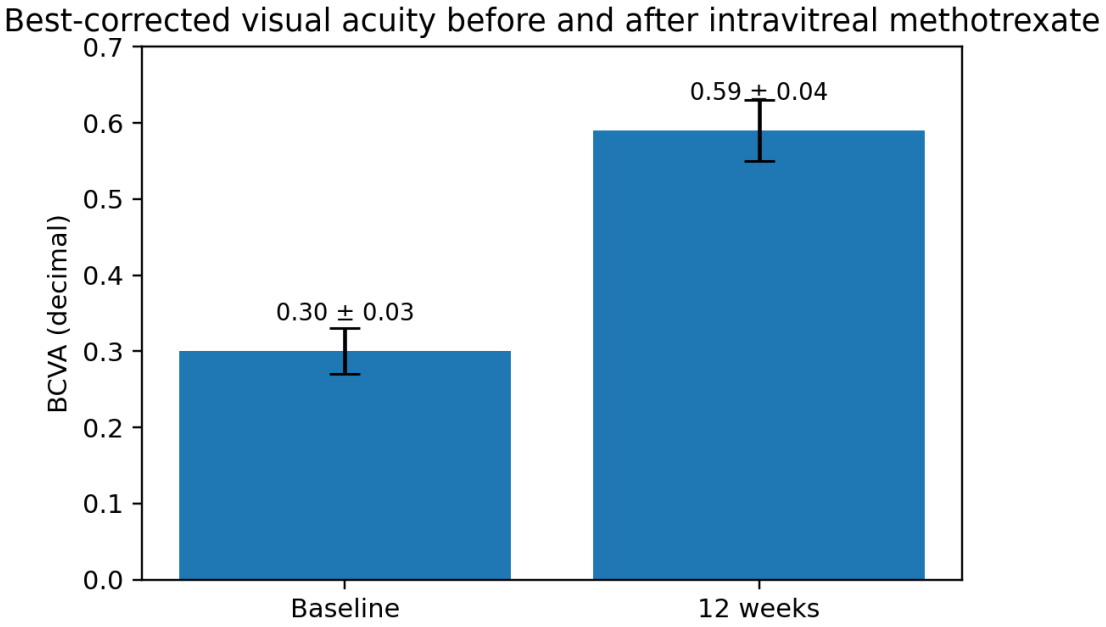

Figure 1. Mean BCVA (decimal) at baseline and 12 weeks after intravitreal methotrexate. Error bars represent SD.

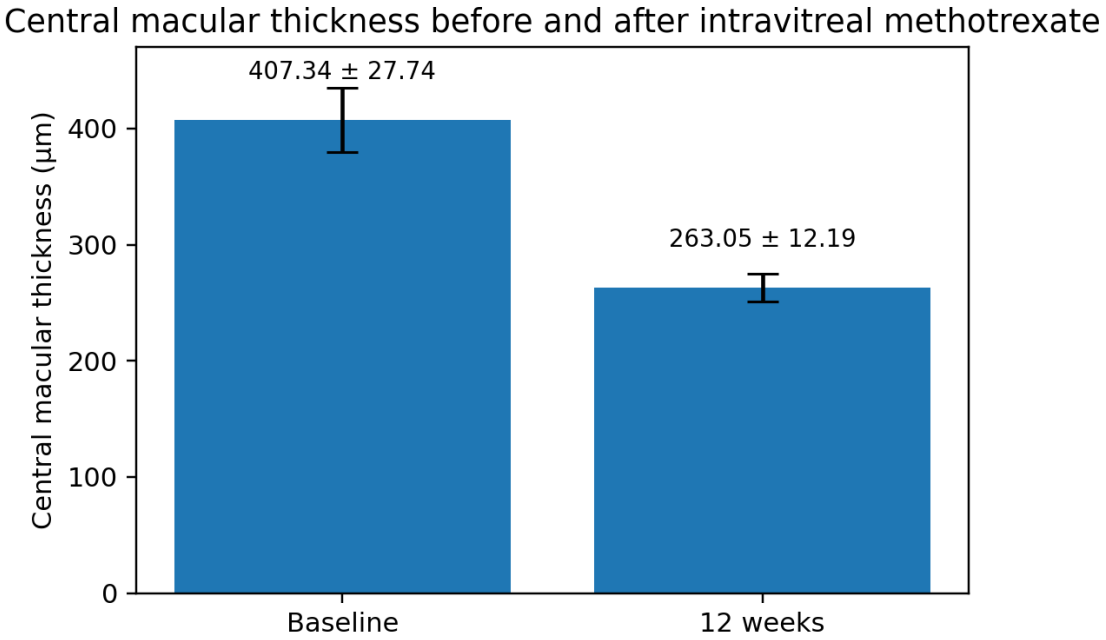

Figure 2. Mean central macular thickness at baseline and 12 weeks after intravitreal methotrexate. Error bars represent SD.

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Exploratory subgroup comparisons are presented in Table 3. At 12 weeks, mean BCVA was higher in patients aged 56–70 years than in those aged 40–55 years (0.61 ± 0.03 vs 0.57 ± 0.04; p<0.001), higher in patients with symptom duration >6 months than ≤6 months (0.603 ± 0.035 vs 0.569 ± 0.028; p<0.001), and higher in patients without diabetes than in those with diabetes (0.600 ± 0.035 vs 0.570 ± 0.031; p=0.001). For CMT, daily computer use >6 hours was associated with a lower 12-week mean CMT (253.75 ± 8.44 µm vs 265.15 ± 11.97 µm; p=0.003). The remaining subgroup comparisons were not statistically significant. Because these analyses compared post-treatment values rather than baseline-adjusted change, they should be regarded as exploratory associations rather than established treatment-effect modifiers.

Table 3. Exploratory comparison of 12-week BCVA and central macular thickness by baseline characteristics.

Variable	Category	BCVA at 12 wk (mean ± SD)	p-value	CMT at 12 wk, µm (mean ± SD)	p-value
Age (years)	40–55	0.57 ± 0.04	<0.001	260.76 ± 10.71	0.073
	56–70	0.61 ± 0.03		266.26 ± 13.57	
Gender	Male	0.586 ± 0.033	0.774	262.97 ± 12.55	0.957
	Female	0.589 ± 0.039		263.14 ± 11.95	
Duration (months)	≤6	0.569 ± 0.028	<0.001	259.93 ± 11.21	0.056
	>6	0.603 ± 0.035		265.71 ± 12.51	
Diabetes mellitus	Yes	0.570 ± 0.031	0.001	263.15 ± 10.06	0.955
	No	0.600 ± 0.035		262.97 ± 13.63	
Hypertension	Yes	0.590 ± 0.027	0.745	265.33 ± 12.57	0.300
	No	0.586 ± 0.041		261.95 ± 11.99	
Smoking	Yes	0.591 ± 0.022	0.769	256.90 ± 8.88	0.083
	No	0.597 ± 0.038		264.16 ± 12.44	
Chronic headache	Yes	0.572 ± 0.025	0.137	258.70 ± 4.37	0.223
	No	0.591 ± 0.037		263.84 ± 12.99	
Contact lens use	Yes	0.603 ± 0.027	0.060	259.47 ± 6.79	0.197
	No	0.583 ± 0.038		264.12 ± 13.26	
Glasses use	Yes	0.591 ± 0.047	0.600	263.26 ± 11.78	0.927
	No	0.586 ± 0.031		262.96 ± 12.48	
>6 h computer use	Yes	0.584 ± 0.032	0.702	253.75 ± 8.44	0.003
	No	0.589 ± 0.038		265.15 ± 11.97	

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DISCUSSION

This case series demonstrated marked short-term functional and anatomical improvement after a single intravitreal methotrexate injection. Mean decimal BCVA increased by 0.29 and mean CMT decreased by 144.29 µm over 12 weeks. These findings support biological activity of intravitreal methotrexate in the study population, but the absence of a comparator means that the magnitude of treatment-specific benefit cannot be separated from regression to the mean, background therapy, variation in inflammatory activity, or other clinical factors. The findings should be interpreted alongside contemporary comparative evidence. In the multicentre MERIT randomized trial, intravitreal methotrexate produced an approximately 11% reduction in central subfield thickness at 12 weeks in eyes with minimally active or inactive uveitis and persistent or recurrent macular edema, whereas dexamethasone implant produced a larger anatomical effect and was the only study arm with a statistically significant average BCVA improvement.8 The present series showed a larger mean proportional CMT reduction (approximately 35.4%), but direct comparison is limited by differences in design, case selection, baseline inflammatory status, outcome definitions, and absence of masking or a control group.

A 2024 systematic review and meta-analysis of non-steroidal intravitreal treatments for non-infectious uveitic CME found improvement in both macular thickness and visual acuity across the pooled literature and included methotrexate among the evaluated therapies; however, the underlying evidence was heterogeneous and comparatively limited for methotrexate.9 Recent reviews similarly describe intravitreal therapy as an attractive local strategy because it can achieve high ocular drug exposure while reducing systemic exposure, but emphasize that treatment choice should be individualized according to uveitis activity, macular edema, ocular comorbidity, prior therapy, and safety considerations (4,6,7,18). The current evidence base for uveitic macular edema remains stronger for local corticosteroid therapy. An American Academy of Ophthalmology assessment published in 2024 concluded that periocular and intraocular corticosteroid approaches improve visual and anatomical outcomes in non-infectious uveitic macular edema, while also highlighting risks such as intraocular pressure elevation and cataract (10). Methotrexate therefore remains of interest as a non-steroidal local option, but this study did not evaluate reduction in systemic or topical corticosteroid exposure and should not be interpreted as demonstrating a steroid-sparing effect.

Earlier clinical reports of intraocular methotrexate described improvement in ocular inflammation, visual acuity, and/or macular edema in selected patients, with some patients experiencing prolonged remission after local treatment (11-14). Studies in Behçet-related posterior uveitis and retinal vasculitis also suggested anti-inflammatory activity of intravitreal methotrexate in selected refractory cases (15,16). These earlier data provided the rationale for subsequent comparative evaluation, but their small sample sizes and heterogeneous indications limit generalizability. The exploratory subgroup findings require particular caution. Higher 12-week BCVA in older patients, those with longer symptom duration, and those without diabetes represents an association with the post-treatment measurement; it does not prove that these groups experienced a greater methotrexate treatment effect. Similarly, the lower 12-week CMT among patients reporting >6 hours of daily computer use is not sufficient to establish a clinically meaningful modifier of treatment response. Baseline-adjusted modelling of change and prespecified subgroup hypotheses would be required to evaluate such questions more rigorously.

From a clinical perspective, the large short-term reductions in CMT and improvement in BCVA observed in this tertiary-care case series justify further study of intravitreal methotrexate in appropriately selected patients. Future work should use standardized uveitis classification, clearly characterize inflammatory activity and uveitis aetiology, employ standardized visual-acuity and OCT outcomes, prospectively monitor ocular adverse events, and compare methotrexate with established local therapies in controlled designs (2,3,8-10).

LIMITATIONS

The study was conducted at a single centre and used a non-probability consecutive sample, which limits external generalizability. Its single-arm design precludes comparative efficacy conclusions and does not control for natural fluctuation of uveitis, regression to the mean, or concomitant clinical influences. Follow-up was limited to 12 weeks after a single injection, so durability of benefit, recurrence, repeat-dosing requirements, and longer-term ocular safety cannot be determined from these results. The analysis combined patients with uveitis and uveitic CME without separate outcome reporting by aetiological or anatomical subtype. BCVA was analysed in decimal notation rather than a logMAR or standardized letter-score format, and the subgroup analyses were exploratory, involved multiple comparisons, and were based on post-treatment values without baseline adjustment. These factors should be considered when interpreting the magnitude and predictors of response.

CONCLUSION

A single intravitreal injection of methotrexate 400 µg/0.1 mL was associated with a significant short-term improvement in BCVA and reduction in central macular thickness at 12 weeks in this case series of patients with uveitis and uveitic cystoid macular edema. The findings support further controlled evaluation of intravitreal methotrexate, while comparative effectiveness, durability, safety, and predictors of response require confirmation in larger prospective studies.

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