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Original article

Intravitreal Methotrexate in Treatment of Non-infectious Uveitic Macular Edema

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ABSTRACT

***Objectives**: To assess the outcomes of the intravitreal administration of methotrexate in noninfectious uveitic macular edema. **Methods.** A prospective interventional case series of patients with noninfectious uveitic macular edema. Twenty-seven eyes of 27 patients were enrolled, intravitreal injections of methotrexate at a dose of 400 mg in 0.1 ml. The primary outcome measure was visual acuity. Secondary outcome measures included control of intraocular inflammation and cystoid macular edema, time to relapse, development of adverse events, and levels of systemic corticosteroid and immunosuppressive therapy. **Results.** Methotrexate proved effective in controlling intraocular inflammation and improving vision in 25 of 27 eyes (92%). The side effect profile was good, with no reported serious ocular adverse events and only one patient having an intraocular pressure of 25 mmHg. Of the 27 eyes that responded to treatment, 2 relapsed (7%), but 23 (92%) entered an extended period of remission. The two eyes that relapsed were reinjected and all responded to treatment. Of the 27 patients on systemic therapy at the start of the study, 19 (70%) were able to significantly reduce this following intravitreal methotrexate injection. **Conclusion.** In patients with uveitis and uveitic cystoid macular edema, intravitreal MTX can effectively improve visual acuity and reduce cystoid macular edema and, in some patients, allows the reduction of immunosuppressive therapy. However, some patients relapse at 3 to 4 months, but a large proportion (92%) enter an extended period of remission of up to 6 months.*

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INTRODUCTION

Uveitis is inflammation of the anterior, intermediate and/or posterior part of the middle coat of the eye (uveal tissue) which can also involves the adjacent structures such as the retina, vessels, vitreous and optic nerve. It can be classified according to etiology in to infectious or noninfectious, idiopathic or secondary to systemic conditions [1].

Posterior uveitis is the major cause of visual deterioration among patients with uveitis, as it may lead to serious complications in form of macular edema, choroidal neovascularization, glaucoma, optic nerve involvement, vitreous opacification, and cataract formation. Among these Macular edemas is the commonest 8.3%. It can lead to visual impairment in about 40% of patients diagnosed with uveitis [2].

Pathophysiology and mechanism of how uveitis can cause macular edema has not been fully understood. The disruption of blood–retinal barrier is engaged in majority of cases which could lead to a disturbance in the

balance between fluid entering the tissues and the function of metabolic pump which in turn end with the accumulation of fluid intra- or extra-cellularly [2]. So, controlling of inflammatory process in noninfectious posterior uveitis is vital to minimize the risk of visual loss [3]. Corticosteroids are the first line therapy for ocular inflammation. However, in situations that require chronic immune suppression, or the side effects of corticosteroids are unsustainable, other treatment modalities are of extreme importance such as immunomodulators [4]. Immunomodulatory agents include the categories of antimetabolites (azathioprine, methotrexate, mycophenolate mofetil), alkylating agents (cyclophosphamide, chlorambucil), T cell inhibitors (cyclosporine, tacrolimus) and cytokines inhibitors such as (interferon alfa). Of these, methotrexate is one of the most commonly used antimetabolites in management of ocular pathology [4].

Methotrexate is an antimetabolite that inhibits DNA replication and RNA transcription through competitive inhibition of the enzyme dihydrofolate reductase [1]. It has been firstly used in treatment of ocular inflammation in 1965 [5].Intravitreal methotrexate (MTX) is a unique option for local treatment that is steroid-sparing, but also immunosuppressive and anti-inflammatory [6].Many studies revealed the use of (400 µg/0.1 ml) of methotrexate intravitreally may be considered an alternative in refractory cases and it seems to offer a longer duration of remission up to 4 months in addition to lowering the risk of ocular hypertension, suggesting it may be a suitable option for glaucomatous patients or those with a history of steroid-induced ocular hypertension [7].Therefore, this pilot prospective study to evaluate the safety, tolerability and potential efficacy of intravitreal injections of intravitreal methotrexate (MTX) for the treatment of non – infectious uveitic macular edema.

METHODS

The study included the 27 patients (27 eyes) who received an intravitreal injection of methotrexate as treatment of non-infectious macular edema in chronic anterior uveitis, intermediate uveitis or parsplanitis, posterior uveitis or pan uveitis and vogt-koyanagi-harada syndrome.

All of the patients were fully informed about the experimental character of the therapy. And they signed an informed consent. All patients have been examined in Aloyun clinic private eye clinic from January 2020 to August 2021, age from 35yrs to 69 yrs, detailed ocular examination performed were best corrected visual acuity BCVA with LogMAR pre and post injections, biomicroscopic examination of anterior segments done to evaluate the ocular inflammation and dilated fundus examination with stereoscopic 66 lens performed. Intraocular pressure pre and post injection was measured by air buff tonometry Tomy. OCT scan done to all patients by Topcon 3D OCT 2000 reading from only right eyes were used in analysis. if there were sever macular edema in one eye the more serious affected eye has been chosen in some patients. Intravitreal methotrexate dose of 400 µg/0.1 mL of MTX was injected intravitreally via the pars plana, 3.5 to 4.0 mm posterior to the inferotemporal limbus using a 27-gauge needle. The given concentration was 2 mg/0.1 ml. we exclude from the study all patients with, glaucoma or any history of ocular surgeries excluded, anterior chamber vascularization and contact lens wearer, eyes with corneal pathologies like pterygium, corneal dystrophies keratoconus, keratoconjunctivitis sicca, ptosis, ocular trauma, Un-known Active or any previous eye infection or inflammation. The primary outcome was the number of participants who meet the definition of treatment success within 12 weeks from baseline, changes in VA and best-corrected visual acuity (BCVA) with LogMAR. Were the Secondary outcomes included the changes in macular thickness, Changes in intraocular inflammation on clinical exam, Observation of dose reductions of systemic immunosuppression or steroids, time to relapse, development of adverse events. Our safety outcomes measurement was included the number and severity of adverse events as systemic and ocular toxicities including cataract progression, vitreous hemorrhage, retinal

detachment, and corneal epitheliopathy. Definition of success for the treatment success is defined as achieving a decreased central macular thickness, Improvement of VA at least 5 lines from baseline pre-injection VA, Control of intraocular inflammation.

Data was presented as frequencies and mean ±SD. Statistical analyses performed by using Statistical Package for the Social Sciences (SPSS version 23.0; IBM Corporation, Armonk, N.Y., USA), α value was 0.01, *P*-values of 0.05 or less will be considered as statistically significant.

RESULTS

Twenty-seven eyes for twenty-seven patients included in this study were 51% females and 48% was males as in table (1) and figure (1) below patients age vary from 35 years to more than 55 years, where the most common age distribution was from 45 to 55 years as in table (2) below.

Table 1. Distribution of patient according to Gender.

Gender	Frequency	Percent	Valid Percent	Cumulative Percent
Males	13	48.1	48.1	48.1
Females	14	51.9	51.9	100.0
Total	27	100.0	100.0	

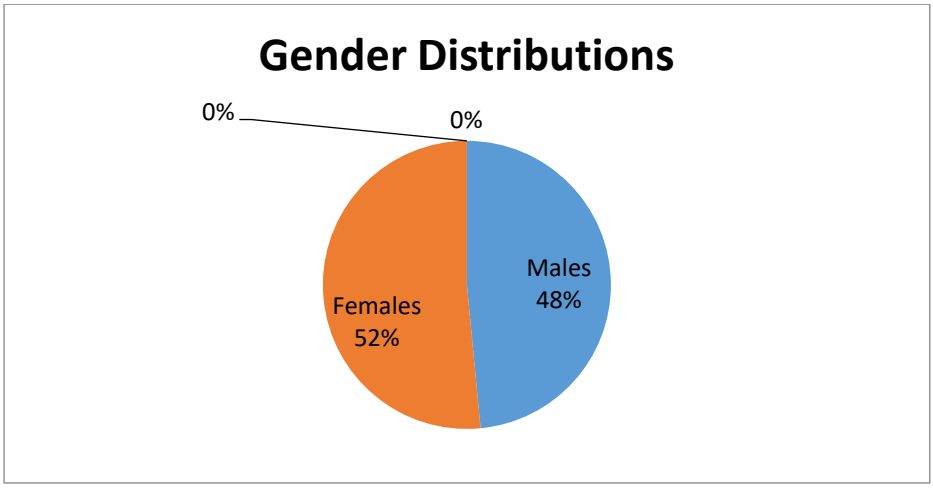

Figure 1. Distribution of patient according to Gender

Table 2. Distribution of patient according to age.

Age range	Frequency	Percent	Valid Percent	Cumulative Percent
From 35 to < 40 yrs	7	25.9	25.9	25.9
From 40 to < 45yrs	1	3.7	3.7	29.6
From 45 to < 50 yrs	8	29.6	29.6	59.3
From 50 to < 55 yrs	9	33.3	33.3	92.6
> 55	2	7.4	7.4	100.0
Total	27	100.0	100.0	

Shapiro-wilk is the used methods in analysis because the sample carrying small numbers it's not carrying abnormal extreme distributions in population samples as show in Table (3) and Fig (2) so the study is statistically significant and carrying actual depending results for practice.

Table 3. Test normality for sample distribution.

Tests of Normality	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
dif1	.148	27	.132	.966	27	.499
a. Lilliefors Significance Correction						

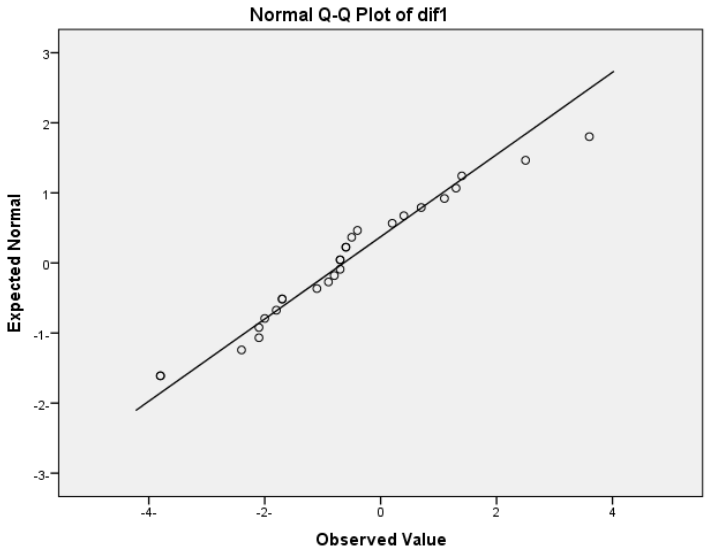

Figure 2. Extend of extremity for sample involved in the study

Observing the IOP measurements pre and post IV MTX injection was not that much raised were its statistically significant as in table (4) were mean for post injection was 18.741 with std deviation 1.8587, and pre injection mean was 18.104 with std deviation 2.0536.

Table 4. IOP measurement post and pre injection

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	99% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Post IOP – pre IOP	.6370	1.7046	.3280	-.2745-	1.5486	1.942	26	.020

Visual acuity improvement noted with injections by comparing pre and post IV metho injection and it was statistically significant with T test and P value as in table (5, 6) and no extremities in normality for sample distribution curve noted as shown in figure (3).

The mean ± SD visual acuity improved significantly (P<.001) from 0.12 ± 0.08 at baseline of the study to a maximum of 0.19 ± 0.14 during the follow-up period. Improvement in visual acuity was statistically significant at the examinations performed 4 weeks (P = .003), 3 months (P = .01), 6 months (P = .03).

Table 5. Significant test normality for sample distribution of VA

Tests of Normality						
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
dif2	.279	27	.000	.784	27	.000

Lilliefors Significance Correction.

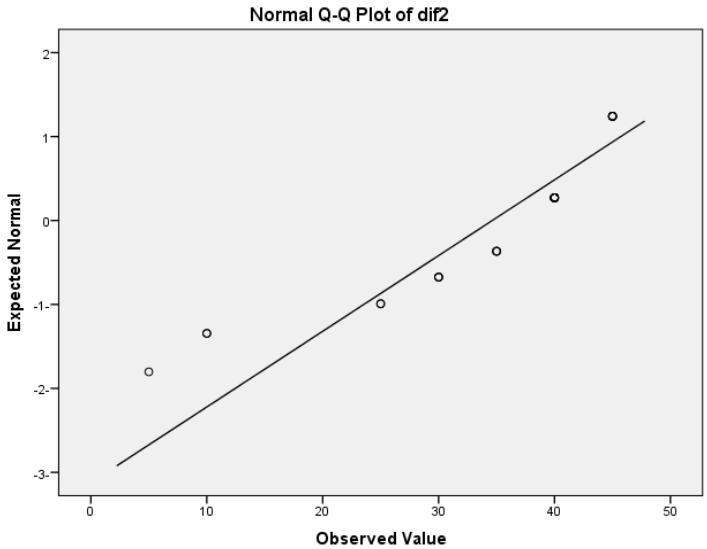

Figure 3. VA distribution and significant improvement of vision after intravitreal injections of methotrexate

Table 6. IMPROVEMENT of VA post injection

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	99% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	postVA - preVA	-34.630-	11.088	2.134	-40.559-	-28.700-	-16.229-	26	.000

As visual acuity improves the Central macular thickness improvement even was noted and its significant with statistical values by compared data in OCT to CMT Pre and Post injection at interval from 4 weeks, 3months, 6 months duration as shown in tables (7,8,9) and figures (4,5,6) below.

Table 7. Improvement of CMT 4 weeks post injection

		Paired Differences					**t**	**df**	**Sig. (2-tailed)**
		Mean	Std. Deviation	Std. Error Mean	99% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	preCMT - postCMT 4wks	582.333	238.810	45.959	454.626	710.040	12.671	26	.000

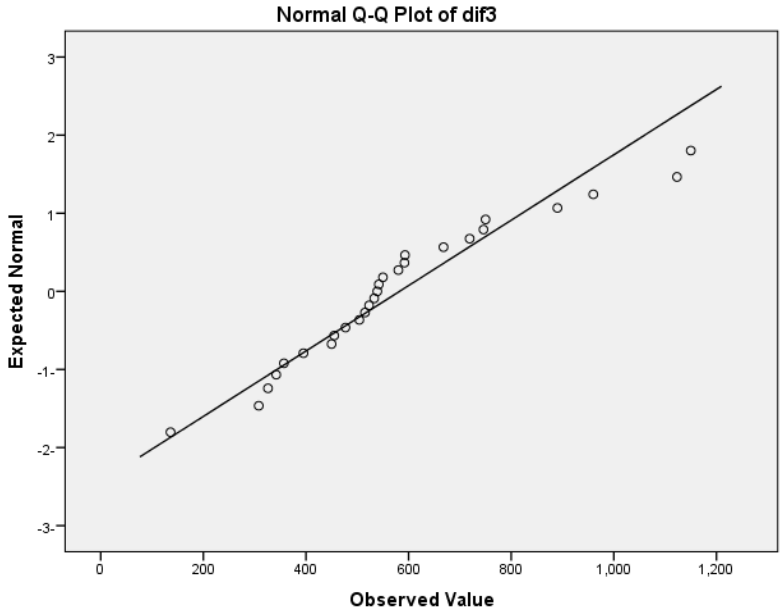

Figure 4. CMT improvement after 4 weeks post injection of MXT

Table 8. CMT improvement after 3 months post injection of MXT

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	99% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	preCMT - postCMT3mon	710.667	248.886	47.898	577.571	843.762	14.837	26	.000

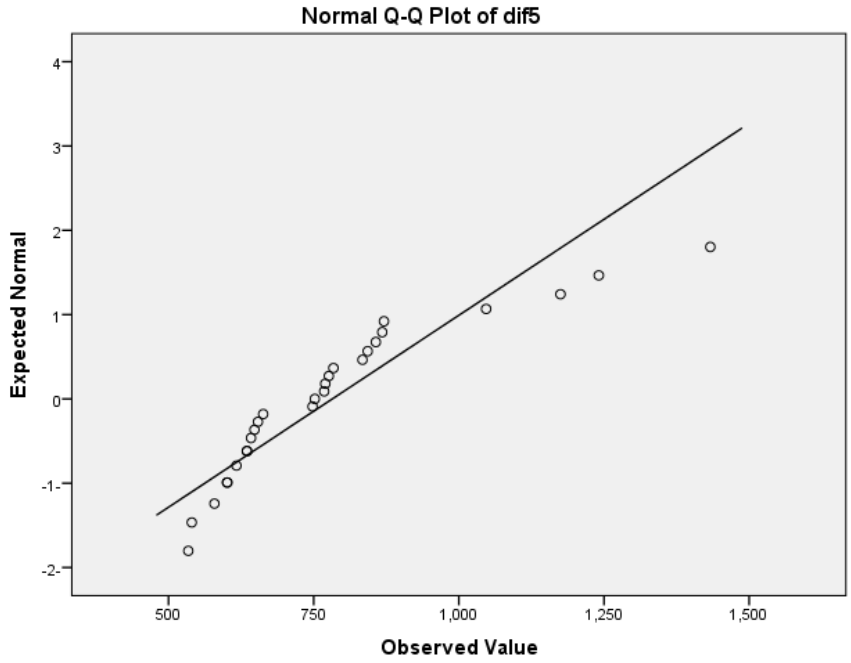

Figure 5. CMT improvement after 3 months post injection of MXT

Table 9. CMT improvement after 6 months post injection

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	99% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	preCMT - postCMT6mon	782.074	219.641	42.270	664.618	899.530	18.502	26	.000

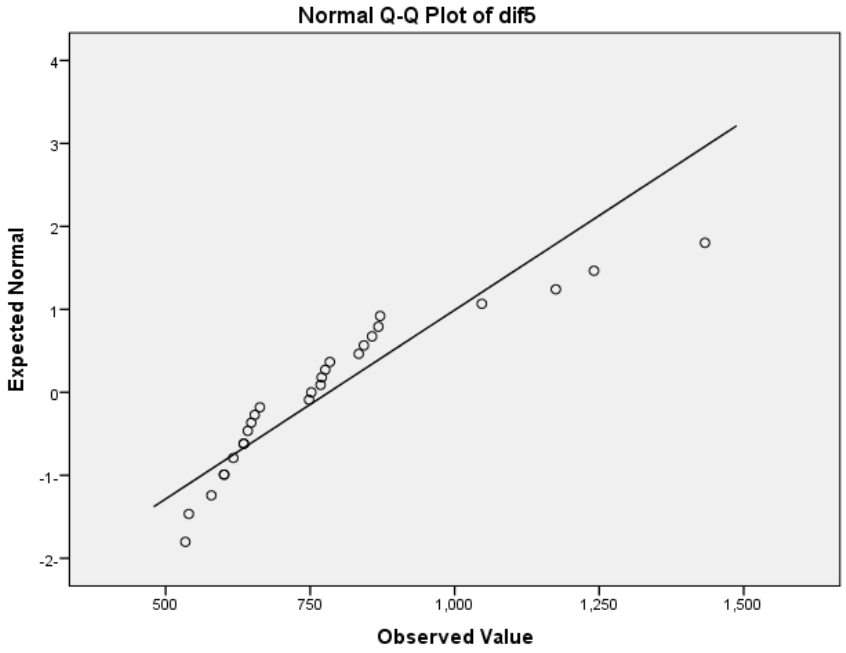

Figure 6. Improvement of CMT continued after following the patients 6 months Post injection

In this study, 92% of eyes responded to the intravitreal methotrexate with improved visual acuity, ocular inflammation, and macular thickness, and 7% of the eyes responded to intravitreal methotrexate relapsed after a median period of 3 months. However, a larger proportion of eyes entered an extended period of remission with no relapses throughout the period of follow-up which was 6 months.19 patients (70%) who were on systemic therapy, were able to reduce their doses. Regarding adverse effects, only one eye had an increased IOP of 25 mmHg, which was controlled with medications.

There is some Complications noted with injection such as one case had vitreous hemorrhage grade II were treated conservatively, two patients had cataract progression and vision deteriorated with follow up after 6 months were decreased VA improvement noted in follow up post injection, corneal epitheliopathy post injection occur in one patient.

DISCUSSION

This study demonstrates the effects of intravitreal methotrexate in patients with uveitic CME and suggests that intravitreal MTX can be an effective treatment for uveitic CME. Twenty-seven eyes for twenty-seven patients included in this patient's age vary from 35 years to more than 55 years.

The mean IOP measurements post and pre-IV MTX injection respectively was 18.741 with std deviation 1.8587, and Pre injection mean was 18.104 with std deviation 2.0536, was within normal so we note that effect of MTX on IOP not that much higher as with TA injections in such cases due to steroid responding.

In this study VA improved after intravitreal MTX in 25 eyes (92%). VA improved significantly at the 4 weeks - 3 and 6-month follow-up examinations. The mean number of relapses decreased significantly after MTX injection ($p= 0.012$).

Our results support another study done by Taylor and associates that was conducted on 15 patients with unilateral uveitis and/or cystoid macular edema. They reported improved VA at all time points that was

statistically significant at the 3- and 6-month follow-up examinations [8]. Even Schlaen et al., retrospective study done in 5 patients and the average post injection CRT was 308±91.04 improve obviously from pre-injection which was 487±44.14 micron and was statistically significant and VA was improved with sign of inflammation [9] and that is support our finding.

Because of deficiency in data done on previous studies about intravitreal methotrexate in uveitic macular edema limited supporting studies facing us in reviewing literature, although case report article by Maab and Mat the note improvement with one patient who had uveitic macular edema and he is steroid responder treated with IV avastin and was not successful after receiving IV MTX dramatic improvement occur in CMT and VA with decreased sign of inflammation and good IOP [10].

In another multi-centre retrospective interventional case series study done by Taylor et al., to assess the outcomes of IV MTX in uveitis in 38 eyes of 30 patients and they conclude that IV MTX can effectively improve visual acuity and reducing cystoid macular edema and extend the remission with reduction of immunosuppressive therapy and that is in agreement with our study [11].So far, the using of Methotrexate because of its rapid onset of effect and the sustained duration of remission with intravitreal therapy stand in contrast to the results achieved with systemic administration, in which it can take up to 6 months for the drug to reach full effect [5].

CONCLUSION

Intravitreal methotrexate appears to be a promising alternative to IV steroids in noninfectious uveitic macular edema especially in steroid responders due to lower risk of increasing IOP and in its effective improvement in CMT.

The extended remission effect by methotrexate in some patients should be explored in future studies. It is imperative to do more studies and monitor the development of adverse events such as corneal decompensation, which may require treatment with topical folinic acid. To establishment of efficacy and safety profile of intravitreal methotrexate & its contraindications of systemic methotrexate also should also be observed by starting a Larger-scale and randomized controlled trials which is definitely required to documentations.

Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

REFERENCES

1. Ng D, Mohamed S, Chu W- kit, Luk FO, Brelén M, Chan CK. Update on the management of non- infectious uveitis. Hong Kong J Ophthalmol [Internet]. 2016Nov.1 [cited 2021Oct.29];20(3):95-105.
2. Shah KK, Majumder PD, Biswas J. Intravitreal therapeutic agents in noninfectious uveitic macular edema. Indian J Ophthalmol. 2018 Aug;66(8):1060-1073. doi: 10.4103/ijo.IJO_35_18. PMID: 30038143; PMCID: PMC6080427.
3. DG Callanan, GJ Jaffe, DF Martin, PA Pearson, TL Comstock: Treatment of posterior uveitis with a fluocinoloneacetonide implant Three-year clinical trial results. Arch Ophthalmol. 2008;126:1191–201.
4. Okada AA. Immunomodulatory therapy for ocular inflammatory disease: a basic manual and review of the literature. Ocul Immunol Inflamm. 2005 Sep-Oct;13(5):335-51. doi: 10.1080/09273940590951034. PMID: 16419419.
5. Gangaputra S, Newcomb CW, Liesegang TL, Kaçmaz RO, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Kempen JH; Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study. Methotrexate for ocular inflammatory diseases. Ophthalmology. 2009 Nov;116(11):2188-98.e1. doi: 10.1016/j.ophtha.2009.04.020. Epub 2009 Sep 12. PMID: 19748676; PMCID: PMC3785935.

6. Oleksandra K, Kapil K. Serial treatment of uveitis with intravitreal injections of Methotrexate during the COVID-19 pandemic. ARVO Annual Meeting Abstract. 2021;62(8):1-28.
7. Sharief LAT, Lightman S, Tomkins-Netzer O. Using Local Therapy to Control Noninfectious Uveitis. Ophthalmology. 2018 Mar;125(3):329-331. doi: 10.1016/j.ophtha.2017.09.033. PMID: 29458826.
8. Taylor SR, Habot-Wilner Z, Pacheco P, Lightman SL. Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema. Ophthalmology. 2009 Apr;116(4):797-801. doi: 10.1016/j.ophtha.2008.10.033.
9. Conrady CD, Yeh S. A Review of Ocular Drug Delivery Platforms and Drugs for Infectious and Noninfectious Uveitis: The Past, Present, and Future. Pharmaceutics. 2021 Aug 8;13(8):1224. doi: 10.3390/pharmaceutics13081224.
10. Maaß J, Matthé E. Intravitreales Methotrexat zur Behandlung eines uveitisch bedingten zystoiden Makulaödems [Intravitreal methotrexate for treatment of uveitic cystoid macular edema]. Ophthalmologe. 2018 Jul;115(7):595-597. German. doi: 10.1007/s00347-017-0548-1.
11. Taylor SR, Banker A, Schlaen A, Couto C, Matthe E, Joshi L, Menezo V, Nguyen E, Tomkins-Netzer O, Bar A, Morarji J, McCluskey P, Lightman S. Intraocular methotrexate can induce extended remission in some patients in noninfectious uveitis. Retina. 2013 Nov-Dec;33(10):2149-54. doi: 10.1097/IAE.0b013e31828ac07d. PMID: 23615343.