Original Article

Topical interferon therapy in uveitic macular edema

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Purpose: To evaluate efficacy of topical interferon alfa-2b (IFN) in the treatment of uveitic macular edema (UME). **Methods:** This is a prospective, interventional case study of patients with UME. Injection IFN was reconstituted into eye drops and a four times/day (QID) application was prescribed. Central macular thickness (CMT) on optical coherence tomography (OCT) scan was evaluated. Improvement in CMT by ≥50 µm from the baseline was studied in eyes with presenting CMT ≥400 µm. **Results:** Twenty eyes of 20 patients with UME were studied: anterior uveitis (n = 3), anterior + intermediate uveitis (n = 5), posterior uveitis (n = 3), retinal vasculitis (n = 3), and panuveitis (n = 6). Mean CMT at the presentation was 423.3 µm (range: 270–604 µm), which improved at 1 month (n = 16), 2 months (n = 10), and ≥3 months (n = 11) follow-up, to 415.3 µm (range: 247–579 µm) (P = 0.411), 364.4 µm (range: 258–566 µm) (P = 0.099), 344 µm (range: 258–484 µm) (P = 0.001), respectively. Twelve eyes of 12 patients had presenting CMT ≥400 µm. In these cases, decrease in CMT by ≥50 µm was seen in 4/10, 4/5, and 5/6 eyes at 1 and 2 months and ≥3 months follow-up. Mean follow-up was 4 months (range: 1–17 months). Complete resolution of UME was seen only in three eyes. No ocular or systemic side effects were observed. **Conclusion:** Topical IFN therapy in QID doses is safe but may have limited role in UME. Long-term therapy may improve its efficacy. Larger studies with dose modification, combination with other drugs, and with homogeneous uveitis population are recommended.

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Interferons (IFN) were discovered in 1957 as natural antiviral substances produced during viral infections.[1] Soon they became popular for their anti-inflammatory property and were found to be useful in the treatment of inflammatory diseases. IFN α has been used in ocular inflammation over the past 3 decades. Systemic administration of IFN has been reportedly successful in the treatment of Behcet's disease refractory to conventional immunosuppressive agents and steroids.[2] Subcutaneous administration of IFN has shown promising results in the treatment of resistant uveitic macular edema (UME).[3] Side effects like flu-like symptoms, invasive procedure, and the cost are major limiting factors for systemic use of IFN. Local routes of administration of IFN have also been attempted in the past. Intravitreal as well as posterior subtenon's injection of IFN has been successfully used in age-related macular degeneration (AMD), for diabetic macular edema and for choroidal neovascular membrane.[4-6] But a report of perilesional IFN injection for ocular surface squamous cell carcinoma has reportedly caused retinopathy.[7] Maleki *et al*.[8] for the first time successfully treated a case of refractory pseudophakic macular edema with topical IFN alpha-2b. Subsequently, its usefulness was confirmed in a small series of patients with pseudophakic CME as well as in a case of post endophthalmitis CME.[9,10] A randomized controlled trial has also demonstrated beneficiary effect of topical IFN in diabetic macular edema although statistically insignificant.[11] The aim of our study was to evaluate efficacy of topical IFN alfa-2b in the treatment of UME.

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Methods

This is a prospective, interventional, longitudinal study conducted at a tertiary care eye center in South India. The study was approved by the internal review board and adhered to the tenets of Helsinki.

Inclusion criteria

Patients diagnosed with UME and advised for topical, systemic, periocular, or intraocular injection of steroids or intravitreal injection of antivascular growth factor (anti-VEGF), or increase in immunomodulatory therapy (IMT).

Patients already on treatment for UME and showing worsening of UME defined as increase in size and number of cystoid spaces and/or any increase in central macular thickness (CMT) as appreciated on spectral-domain optical coherence tomography (SD-OCT) scan after 3–4 weeks of the previous treatment.

Exclusion criteria

Patients with anterior chamber and/or vitreous cells more than 0.5 or clinically appreciated inflammatory signs other than UME requiring immediate therapeutic intervention with steroids or IMT; overlapping UME with other etiology (e.g. diabetic macular edema); vitreomacular traction demonstrated

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in SD-OCT scan; current IFN therapy for any reason; and follow-up less than one month were excluded.

Patients fulfilling the above criteria were offered alternative therapeutic option of "topical IFN therapy" against conventional treatment for UME vide supra. Patients who consented were enrolled in the study. Patients who did not show improvement in UME in 1 month were offered study exit versus further continuation of trial after explaining pros and cons. Patients with relapsing uveitis during follow-up, which needed increase in IMT and steroids and patients who opted for conventional treatment during the follow-up exited the study.

IFN eye drops were prepared from commercially available subcutaneous injection IFN Alfa-2b 3 MU/mL (Inj. Intalfa™).[9] The drug was diluted using 2 mL of sterile water for injection to constitute 3 mL IFN (1 MU/mL) eye drop solution. Patients were handed over the freshly prepared IFN eye drops in an ice pack with the instruction of storage in the refrigerator door at 4°C and to apply 1 drop four times per day (QID) to the affected eye. Patients who were on IMT were advised to continue the medications in same doses. After commencing IFN therapy, patients on oral and topical steroids were advised to taper by 10 mg per week or 1 drop per week, respectively, and stop. Nonsteroidal anti-inflammatory drugs (NSAIDs) discontinued after witnessing 1st improvement on SD-OCT scan within a month. After 1st complete resolution of UME, IFN was tapered by 1 drop per month.

All the patients underwent slit-lamp biomicroscopy on all visits and indirect ophthalmoscopy where needed. Corrected distant visual acuity (CDVA), intraocular pressure (IOP), and SD-OCT scan were done at the baseline, 4 weeks, and when needed. CMT was noted as on thickness map using Heidelberg™ OCT software. In eyes with CMT ≥ 400 μm at the presentation, improvement of ≥ 50 μm was studied during the follow-up. Patients with more than 3 months of follow-up with IFN therapy, lowest CMT achieved was noted. A subgroup analysis for pseudophakic and phakic patients was also done.

Statistical analysis: All data were entered in Microsoft Excel 365. The data were checked for normality using the Shapiro–Wilk test. Comparison of means for paired samples was done by using the paired samples *t* test. A *P* value of less than 0.05 was considered significant.

Results

Twenty eyes of 20 patients were included in the study. Mean age of presentation was 50.65 years (range: 18–77 years). Eight were males and 12 were females. Mean baseline CDVA ($n = 18$) was 20/50 (range: 20/30–20/200). Mean baseline intraocular pressure (IOP) ($n = 19$) was 14.7 mmHg (range: 7–27). Twelve eyes (60%) were pseudophakic and one had posterior capsular opening. The diagnosis of uveitis and medications at the time of enrolment into the study and the previous medications given for UME were as shown in Table 1. Eight eyes had vitreous cells not exceeding 0.5. At 1-month follow-up ($n = 14$) mean IOP was 13.4 mmHg (range: 10–19 mmHg) and at the final follow-up ($n = 16$) IOP was 15.1 mmHg (range: 10–24 mmHg). Fundus fluorescein angiography was done in 10 cases before enrollment: four vasculitis, five anterior + intermediate uveitis, and one anterior uveitis. Hyperfluorescence suggestive of macular edema was seen in all cases. In addition, inflammatory small vessel leakage was observed in eight cases.

Mean CMT at the presentation was 423.3 μm (range: 270–604 μm). At 1-month ($n = 16$), [Table 2] 2 months ($n = 10$), and at ≥ 3 months ($n = 11$) follow-up the mean CMT improved to 415.3 μm (range: 247–579 μm) ($P = 0.411$), 364.4 μm (range: 258–566 μm) ($P = 0.099$), 344 μm (range: 258–484 μm) ($P = 0.001$), respectively. Increase in CMT was seen in 6/16 patients (37.5%) by a mean of 39.5 μm (range: 10–73 μm) at 1 month and in 3/10 (30%) by a mean of 33.66 μm (range: 4–78 μm) at 2-months follow-up.

At the presentation, 12 eyes had CMT ≥400 μm. In those eyes, decrease in CMT by ≥50 μm was seen in 4/10 (40%), 4/5 (80%), and 5/6 (83.3%) eyes at 1 month and 2 months and ≥3 months follow-up [Table 3]. Mean follow-up in those cases was 2.3 months (range: 1–4 months) [Fig. 1].

Mean follow-up for 20 cases was 4 months (range: 1–17 months). Four patients had 1 month while the rest had more than 1 month follow-up, three were lost to follow-up,

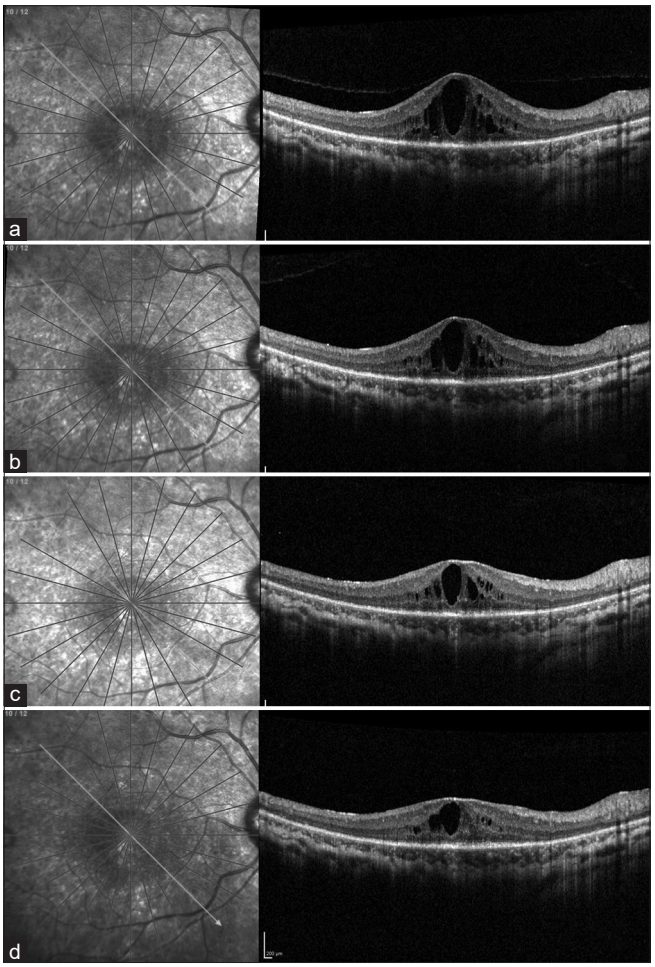

Figure 1: Case 2, a 30-year-old female, known case of VKH disease on 20 mg of methotrexate since 1 year and off steroids since 8 months developed macular edema. SD-OCT scan of the right eye at the enrolment of the study shows CMT 528 μm (a), after 2 weeks of IFN therapy, CMT decreased to 484 μm (b) and after 1 month to 459 μm (c) and after 3.5 months the CMT was 369 μm (d)

Table 1: Demographics, diagnosis, medications, and follow-up

Case	Age/ Sex	Diagnosis	Medications at enrollment with duration (months)	Previous medications for CME with washout period (months)	Follow-up with IFN (Month)	Study exit reason
1	58/M	AU+IU	Nepa (5), Timo (20), MTx (17)	IVTA (28), PST (17)	7	No improvement
2	30/F	VKH	MTx (17)	Nil	3.5	Lost to follow-up
3	18/F	AU+IU	Pred e/d (1), T.Defcort (3), Nepa (1), Dorzo (3), Timo (3), Diamox (1)	Nil	1	Lost to follow-up
4	60/F	VKH/ Sarcoidosis	Nepa (2), Brimo (2), Timo (2)	Pred e/d (1)	6	Improved
5	59/F	ARN	Nepa (12), Pred e/d (1), T. Defcort (1)	Bevacizumab (3)	1	No improvement
6	33/F	RV	Nepa (1), T. Pred (2)	Bevacizumab (5)	2	No improvement
7	28/F	RV	Nepa (6), Brimo (4), Timo (4)	IVTA (9)	2.5	No improvement
8	54/F	AU+IU (Sarcoid/TB)	Nepa (1)	Nil	1	Relapse of uveitis
9	37/M	AU	Nil	Pred e/d (8), T. Pred (8)	4	Lost to follow-up
10	44/F	Panuveitis	MTx (34)	Nil	1.5	Relapse of uveitis
11	74/M	AU	Pred e/d (1.5)	Ranibizumab (13), IVTA (24)	1	No improvement
12	51/M	Sarcoidosis/TB	Nil	Pred e/d (1), Nepa (1)	1.8	No improvement
13	52/M	RV	Nepa (1), AZA (36)	Bevacizumab (12)	17	No improvement
14	81/M	AU	Pred e/d (2)	Nil	5	Improved
15	70/F	Panuveitis (MFC)	MTx (4), Nepa (5), Dorzo (7), Timo (7), Brimo (5)	PST (6)	8	No improvement
16	41/M	VKH	MMF (10), T. Pred (4)	Nil	4	Improved, Relapse of uveitis
17	56/F	AU+IU	Brimo (18), Timo (18)	Nepa (1)	3	No improvement
18	26/F	OIS- Takayasu Disease	MMF (24), Dorzo (24), Timo (24), Brimo (24)	Nil	3.5	No improvement
19	64/F	Resolved ER suspect	Nepa (3)	AZA (5), T. Pred (6)	6	Lost to follow-up
20	77/M	AU+IU	T. Defcort (3), Nepa (2)	Nil	1.3	No improvement

M, Male; F, Female; AU, Anterior uveitis; IU, Intermediate uveitis; VKH, Vogt Koyanagi Harada disease; ARN, Acute retinal necrosis; RV, Retinal vasculitis; MFC, Multifocal choroiditis; OIS, Ocular ischemic syndrome; ER, Epidemic retinitis; MTx, methotrexate; AZA, Azathioprine; MMF, Mycophenolate mofetil; Pred, Prednisolone; Defcort, Deflazacort; e/d, eye drops; Nepa, Nepafenac; Timo, Timolol; Dorzo, Dorzolamide; Brimo, Brimonidine; IVTA, Intravitreal Triamcinolone Acetonide; PST, Posterior subtenon's injection of triamcinolone acetonide.

three had uveitis relapse, and nine had no improvement and exited study at variable duration [Table 1] Complete resolution of UME was seen only in three eyes (case 4, 14, and 16). The resolution occurred at 4, 5, and 3.5 months respectively. In case 4 and 14, no recurrence of UME was noted in 1 month of follow-up after the resolution, whereas in case 16, uveitis relapsed while on IFN therapy and had to exit from the study although no recurrence of UME was noted. In cases with angiographic leakage (n = 8) before enrollment, at 1-month follow-up CMT improved in 4/6 cases and at 2-months follow-up in 2/4 cases but none had complete resolution.

Comparing pseudophakic eyes (n = 10) and phakic eyes (n = 6) with 1-months follow-up, mean CMT at the presentation was 408 µm (range: 270–604 µm) in pseudophakics and 455 µm (range: 276–562 µm) in phakic eyes. At 1-month follow-up mean CMT in pseudophakic eyes was 421 µm (range: 272–579 µm) and in phakic eyes was 405.5 µm (range: 264–502 µm). Improvement of ≥50 µm (range: 50–98 µm) in CMT was seen only in four phakic eyes.

None of the patients had any ocular side effects related to IFN. Patients complain of no systemic side effects during the treatment period. Medications discontinued during the IFN therapy are listed in Table 1. Mean CDVA at the final follow-up (n = 17) was 20/40 (range: 20/20–20/114). Ellipsoid zone disruption was observed in four eyes at the enrollment remained status quo during follow-up.

Discussion

We evaluated the efficacy of topical IFN alfa-2b in UME. Various types of anterior, intermediate, posterior, and panuveitis cases were studied [Table 1]. At the enrollment, in all cases, presence of inflammation observed clinically (except for the sign of UME) did not warrant an increase in IMT or steroids. Thus, we studied the cases where uveitis was clinically under control except for the presence of UME. After commencing the IFN therapy, steroids were tapered further and IMT was continued in same doses. To study quantitative improvement in the CMT, we analyzed eyes with CMT ≥400 µm at the presentation and studied the number of eyes showing reduction in CMT by ≥50 µm. This was based on the previously reported study by Afarid *et al.*,[11] who observed 53.1 ± 153 µm improvement in their patients with diabetic macular edema after a month of IFN use in QID doses.

We observed that addition of IFN therapy made insignificant improvement in the UME at 1-month and 2-months follow-up. Only three patients showed complete resolution of UME. At 1-month follow-up, we observed improvement as well as worsening in few cases [Table 2]. We also observed that eyes with longer follow-up (≥3 months) with IFN therapy showed more improvement [Table 3].

Systemic use of IFN is well known in uveitis, but very few studies have been done with its topical application. The very first use of topical IFN was done in peudophakic macular edema, which showed complete resolution after 3 months of continuous use in QID doses.[8] Thereafter, the drops were tapered by 1 drop per 8 weeks. Unfortunately, in our cases, such tapering was not possible as the UME never resolved completely in most of the patients. In case 4 with complete resolution, the patient discontinued the therapy after 4 months and was reviewed after a month. No recurrence was seen. Case 14 that demonstrated complete resolution had lost to follow-up after resolution, whereas in case 16 although UME resolved, uveitis relapsed during the follow-up and had to exit the study.

A small case series of eight patients with pseudophkic macular edema has demonstrated dramatic improvement within a month, which was presumed to be related with posterior capsular opening.[9] Post endophthalmitis chronic macular edema has also shown complete resolution with topical IFN therapy without recurrence.[10] In this case, the therapy was commenced after the cataract surgery, hence it remained unknown if the same response could have been observed with phakic eye. Even in the randomized control trial of topical IFN for diabetic macular edema, pseudophakic status and resolution of macular edema were not evaluated.[11] In our study, although more than 50% of patients were pseudophakic, all except one (case 14) had intact posterior capsule. One may speculate the delayed response in our cases with intact posterior capsule or phakic status. But our study showed 50 μm or more decrease in CMT at 1 month follow-up in four phakic eyes against none in pseudophakics. Larger studies are needed to evaluate penetration of topical IFN into the posterior segment in phakic, pseudophakic, and pseudophakic eyes with posterior capsular opening.

Table 2: Therapeutic response to topical IFN

Case	CMT at baseline (μm)	CMT at 1 month (μm)	Lowest CMT achieved when F/U ≥ 3 month (μm)
1	440	490	258
2	528	459	369
3	415	365	N.A.
4	404	N.A.	309
5	444	468	N.A.
6	562	484	484
7	492	502	479
8	491	505	N.A.
9	457	359	359
10	493	N.A.	N.A.
11	604	579	N.A.
12	516	511	N.A.
13	382	N.A.	356
14	373	351	336
15	359	425	299
16	374	N.A.	286
17	294	272	N.A.
18	292	365	N.A.
19	276	264	250
20	270	247	N.A.

CMT, Central macular thickness; F/U, Follow-up; N.A., Not available/Not applicable

Multiple factors can be considered for poorer or slower response to topical IFN in uveitis apart from the drug penetration. Although subclinical, the severity of inflammation in UME could have been more compared with the pseudophakic macular edema. The inflammatory mediators responsible for UME could be different than that of pseudophakic macular edema.[9] In contrast to pseudophakic macular edema, uveitis may have waxing and waning course. Recurring inflammation in posterior or panuveitis may not be prevented by topical anti-inflammatory therapy. In our study, during the course of IFN therapy, the uveitis did relapse in few. Thus, the course of the disease for pseudophakic macular edema and UME is different signifying different response to the topical IFN. Adherence or compliance to topical medication is another major factor that can influence therapeutic outcome. Maintaining temperature-controlled storage can be a challenge for some patients. And finally the QID dose of topical IFN would have not been adequate for UME in contrast to the pseudophakic macular edema.

Side effects of systemic IFN therapy such as fatigue, flu-like symptoms, as well as IFN-induced retinopathy are known, but uveitis caused by systemic IFN therapy has also been reported. Doycheva *et al*.[12] have described three cases of sarcoid-uveitis presumably caused by systemic IFN therapy. In our series, we had only one case of suspected sarcoid-uveitis who received topical IFN therapy for 6 months and no recurrence of uveitis was seen during the therapy, but the patient developed recurrence 10 months after discontinuation of topical IFN therapy. No other patient developed sarcoid-like uveitis neither in our series nor in the reported series of topical IFN therapy.[8-11]

Our study was limited with small numbers, short, and irregular follow-ups after 1 month. This created difficulty in studying the exact duration of maximum improvement. Most of our cases were already on treatment at the enrollment. Although we documented inefficacy of the prior treatment by considering the duration of the therapy and the persistence

Table 3: Assessment of CMT reduction by ≥50 μm in patients with CMT ≥400 μm at presentation

	Improved by ≥50 μm		Worsened by ≥50 μm	
Follow-up	At 1 month (*n*=10)	At ≥3 months (*n*=6)	At 1 month (*n*=10)	At ≥3 months (*n*=6)
Number of cases improved	4 (40%)	5 (83.3%)	1 (10%)	0 (0%)

of UME, the synergistic effect of IFN with previous therapy remains unknown, which perhaps may create a bias. There was also a bias created due to the inclusion of different types of uveitis regardless the etiology. Similar to the randomized control trial by Afarid *et al*.,[11] our study also lacked estimation of the drug penetration in the posterior segment. The strength of our study is that we contributed 20 more cases to previous sparsely reported studies on topical IFN therapy in macular edema and reiterate its safety profile.

Conclusion

Our study has shown that topical IFN therapy although a novel alternative for conventional treatment for macular edema, has a limited role in UME in QID doses, but its long-term use could be beneficial against its short-term use. Studying intraocular penetration, dose modification, combination with other drugs and studying its efficacy separately for different uveitic entities may explore new avenues for its use in uveitis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev 2001;14:778-809.
2. Tugal-Tutkun I, Güney-Tefekli E, Urgancioglu M. Results of interferon-alfa therapy in patients with Behçet uveitis. Graefes Arch Clin Exp Ophthalmol 2006;244:1692-5.
3. Deuter CM, Koetter I, Guenaydin I, Stuebiger N, Zierhut M. Interferon alfa-2a: A new treatment option for long lasting refractory cystoid macular edema in uveitis? A pilot study. Retina 2006;26:786-91.
4. Kertes PJ, Britton WA Jr, Leonard BC. Intravitreal interferon alpha-2b for the treatment of neovascular age-related macular degeneration: A pilot study. Can J Ophthalmol 1997;32:185-8.
5. Cellini M, Balducci N, Strobbe E, Campos EC. Subtenon injection of natural leukocyte interferon α-2a in diabetic macular edema: A case report. BMC Ophthalmol 2013;13:63.
6. Cellini M, Strobbe E, Balducci N, Campos EC. Effect of subtenon injection of natural leucocytic interferon-α for treatment of age-related choroidal neovascularization. Acta Ophthalmol 2011;89. doi: 10.1111/j. 1755-3768.2011.345.x.
7. Dalla S, Champion M, Ajlan R, Sutphin JE, Sokol JA. Unilateral retinopathy post perilesional interferon α2b injections for ocular surface squamous cell carcinoma. Am J Ophthalmol Case Rep 2021;27:101196.
8. Maleki A, Aghaei H, Lee S. Topical interferon alpha 2b in the treatment of refractory pseudophakic cystoid macular edema. Am J Ophthalmol Case Rep 2018;10:203-5.
9. Kawali A, Snehith R, Singh V, Sanjay S, Mahendradas P, Shetty R. Topical interferon – A novel treatment for pseudophakic macular edema. Indian J Ophthalmol 2021;69:2355-60.
10. Kawali A, Srinivasan S, Mahendradas P, Shetty R. Topical interferon in recurrent inflammatory macular edema following a cat bite. Eur J Ophthalmol 2021;14:11206721211024809.
11. Afarid M, Meshksar A, Salehi A, Safarpour MM. Evaluation of the effect of topical interferon α2b as a complementary treatment of macular edema of patients with diabetic retinopathy: A double-blind placebo-controlled randomized clinical trial study. Retina 2020;40:936-42.
12. Doycheva D, Deuter C, Stuebiger N, Zierhut M. Interferon-alpha-associated presumed ocular sarcoidosis. Graefes Arch Clin Exp Ophthalmol 2009;247:675-80.