Original Article

Topical interferon – A novel treatment for pseudophakic macular edema

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Purpose: The aim of this study was to evaluate the efficacy of topical interferon (IFN) therapy in pseudophakic cystoid macular edema (P-CME). **Methods:** This is a prospective, interventional case series of patients with P-CME. Patients presenting with P-CME were given the option of topical IFN therapy against conventional treatment with oral, topical, intravitreal, and periocular steroid therapy and antivascular growth factors. Patients who consented for the same were advised to use the IFN drops four times/day. Commercially available injection IFN alfa-2b was reconstituted to prepare the eye drops (1 MIU/ml). Optical coherence tomography (OCT) was done at the baseline and on each review visit until complete resolution of P-CME. **Results:** Eight eyes of eight patients diagnosed with P-CME were studied. Mean central macular thickness (CMT) on OCT at the presentation ($n = 8$) and at 4 weeks post topical IFN therapy ($n = 6$) was 560.1 µm (range: 349–702 µm) and 344.33 µm (range: 250–390 µm), respectively. All eyes except one had posterior capsular rent (PCR). Five patients had regular follow-up until resolution. The mean duration of complete first resolution of P-CME was 5 weeks (range: 4–7.1 weeks) in those patients. Relapse was seen in three patients who responded after resuming or continuing the therapy. Case 1 had 9 months follow-up after completion of IFN therapy, and no recurrence was noted. No ocular or systemic side effects related to the topical IFN therapy were noted clinically, except papillary conjunctivitis in one patient. **Conclusion:** Topical IFN therapy can be a noninvasive, economical, and effective choice of treatment for P-CME, especially in the case of PCR, and where steroids are contraindicated.

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Pseudophakic cystoid macular edema (P-CME) post intraocular surgery remains a frequently seen complication in clinical practice. Nonsteroidal anti-inflammatory drugs (NSAIDs), topical, oral, periocular, and intraocular steroids as well as carbonic anhydrase inhibitors or combination therapy have been used in the past for the treatment of P-CME.[1,2] Failure of topical NSAIDs in the treatment of P-CME is not uncommonly seen in clinical practice. Although steroids are highly efficacious, clinicians may hesitate to use them when infections are not completely ruled out or if they are contraindicated due to steroid response. Antivascular endothelial growth factors (anti-VEGF) gained popularity as a steroid-sparing agent in the treatment of P-CME over the past decade.[3] But the cost and the invasive nature of the therapy hinder its use in many patients. Recently a randomized controlled trial in diabetic macular edema and a single case report of P-CME have reported favorable response to topical interferon (IFN) therapy.[4,5] Although systemic use of IFN is well-known in ocular inflammation and macular edema,[6-9] literature on topical IFN therapy for P-CME is scarce. We hereby report a series of eight cases of P-CME, which showed favorable response to the topical IFN therapy.

Methods

This is a prospective, interventional, longitudinal study conducted at a tertiary eye care center in South India. The study was approved by the internal review board, and the study adhered to the tenets of the Declaration of Helsinki. Patients diagnosed with P-CME and advised for conventional therapeutic measures such as intravitreal injections of steroids, anti-VEGFs, and oral steroids were given the option of a novel topical IFN therapy after explaining its off-label use. The patients who consented for the same were enrolled into the study. Commercially available injection IFN alfa-2b measuring 3 million international units (MIU)/mL (Intalfa(R), Intas Pharmaceuticals Ltd. India) was reconstituted by diluting it with 2 mL of distilled water to form 3 mL of eye drops (1 MIU/mL). The cold chain was maintained with ice packs during the transport, and the patients were instructed to store the drops in the refrigerator door at 4°C and start using it four times/day. Spectral domain optical coherence tomography (SD-OCT) was done at the baseline and on each review visit until the complete resolution of the P-CME wherever possible. Central macular thickness (CMT) on SD-OCT scan was noted as measured automatically on thickness map using Heidelberg™ Eye Explorer software. Corrected distant visual acuity (CDVA), intraocular pressure measurement, and the clinical examination were repeated during each visit. Weeks taken for first complete resolution were noted for the patients who had SD-OCT done at 2 and/or at 4 weeks after commencing IFN therapy. Complete

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resolution of CME was defined as the absence of intraretinal hyporeflective cystic spaces and the absence of subretinal fluid on the SD-OCT scan. Approval from ethics committee was obtained and the date of final approval was: 24.9.20.

Results

Eight eyes of eight patients diagnosed with P-CME were studied. The mean age at the presentation was 58.7 years (range: 48–67 years). Six were males and two were females. All eyes except one (Case 8) had posterior capsular rent (PCR). Mean CMT on SD-OCT scan at the presentation (n = 8) was 560.1 μm (range: 349–702 μm) [Table 1]. At 2 weeks post topical IFN therapy (n = 6), mean CMT improved to 422.3 μm (range: 333–501 μm) and at 4 weeks it decreased to 344.33 μm (range: 250 – 390 μm). Five patients had regular follow-up (with SD-OCT scan done at 2 and 4 weeks of starting IFN) until resolution or more. Mean duration of complete resolution of P-CME was 5 weeks (range: 4–7.1 weeks) in those patients [Table 1]. Three eyes had CME of >500 μm at presentation. Thirty percent reduction was observed in 2 to 4 weeks in these cases. No ocular or systemic side effects related to the topical IFN therapy were noted clinically, except in Case 7 who developed papillary conjunctivitis after a month.

Case 1: A 63-year-old man presented with P-CME 6 months post cataract and subsequent vitrectomy surgery done elsewhere in the left eye (OS), details of which were unavailable. His CDVA was 20/125. Intraocular pressure (IOP) was 6 mmHg. Slit-lamp examination of OS showed 2+ cells in the anterior chamber (AC), pseudophakia with PCR, 1+ vitritis, dull foveal reflex, and otherwise normal fundus examination. OCT showed minimal CME. AC tap (smear, culture, molecular diagnostics for eubacterial genome, *Propionibacterium acnes*, and panfungal genome) was negative for organisms. Patient received three doses of intravitreal vancomycin, ceftazidime, and dexamethasone, along with topical bromfenac (0.09%) three times/day, topical prednisolone acetate (1%) four times/day (QID), followed by oral corticosteroid (40 mg) in tapering doses. But after steroid taper, CME recurred twice, which responded to intravitreal triamcinolone acetonide (IVTA). Last IVTA was given 3 months prior, patient had stopped topical steroids 2 months before, and he was on topical bromfenac only at the enrollment into the study. At his third recurrence, SD-OCT scan showed CMT of 628 μm [Fig. 1a]. The patient was offered a novel therapeutic option of topical IFN therapy, to which he agreed and consented. Dramatic improvement was observed within 1 week. CMT decreased to 413 μm [Fig. 1b]. Bromfenac eye drop was discontinued after 2 weeks. QID dosing of topical IFN was continued for 6 weeks followed by three times/day (TID) for 3 months. After 4 months of topical IFN monotherapy, there was no sign of inflammation, and SD-OCT confirmed resolution of macular edema [Fig. 1c]. CDVA in OS improved to 20/30. IOP remained under control, and no side effects attributed to IFN were noted. Further, IFN was tapered 1 drop per month and stopped. The patient was reviewed 9 months after stopping the IFN therapy. No relapse of P-CME was noted.

Case 2: A 61-year-old man presented with P-CME 4 months after cataract surgery in OS. The patient was treated elsewhere with topical and oral corticosteroids 3 months ago (details were not available), and he was also on brimonidine 0.2% eye drops two times/day. At presentation, he was off all the medications for a week. His CDVA in OS was 20/60. IOP was 16 mmHg in OU. Examination of OS revealed mild congestion, mild corneal epithelial edema, quiet AC, anterior chamber intraocular lens (IOL) with a large PCR, and normal fundus examination but CME. Patient was diagnosed as P-CME with early pseudophakic keratopathy. SD-OCT showed CMT 699 μm [Fig. 2a]. Patient consented for the IFN trial. One month use of topical IFN monotherapy (in QID dose) resulted in complete resolution of the CME [Fig. 2b]. Further, the patient was lost to follow-up due to COVID-19 (coronavirus disease 2019)

Table 1: Therapeutic response to topical interferon in pseudophakic macular edema

Case	CMT at presentation (μm)	CMT at 2 weeks (μm)	CMT after 1 month (μm)	CMT at resolution (μm)	Weeks for complete resolution	Known duration of CME before IFN (weeks)	Treatment before IFN therapy	Follow-up after starting IFN (months)	Recurrences
1	628	400	390	342	7.1	64	i/vit V C D (3), bromfenac e/d, prednisolone e/d and tab., IVTA (2)	14	Nil
2	699	550	377	367	4	12	Steroid e/d and tab.	6	1
3	563	N.A.	N.A.	275	N.A.*	2	Dexamathasone e/d, nepafenac e/d	3	Nil#
4	702	400	350	350	4	6	IVTA (1)	2.5	1#
5	349	333	329	N.A.	N.A.#	8	Bevacizumab (1), IVTA (1)	3	Nil#
6	478	350	250	250	4	0	Nil	3.5	Nil
7	585	501	370	370	6	0	Nil	2.5	Nil#
8	477	N.A.	N.A.	358	N.A.*	1	Prednisolone e/d, nepafenac e/d	8	2#

CMT: Central macular thickness on OCT scan, N.A: Not available/Not applicable. CME: Cystoid macular edema, IFN: interferon, i/vit: intravitreal, V C D: Vancomycin, Ceftazidime, Dexamethasone, IVTA: intravitreal triamcinolone acetonide, e/d: eye drops, tab.: tablets. *Exact duration of resolution remained unknown as OCT scan was not available at 2 and 4 weeks. #Case under follow-up on IFN therapy

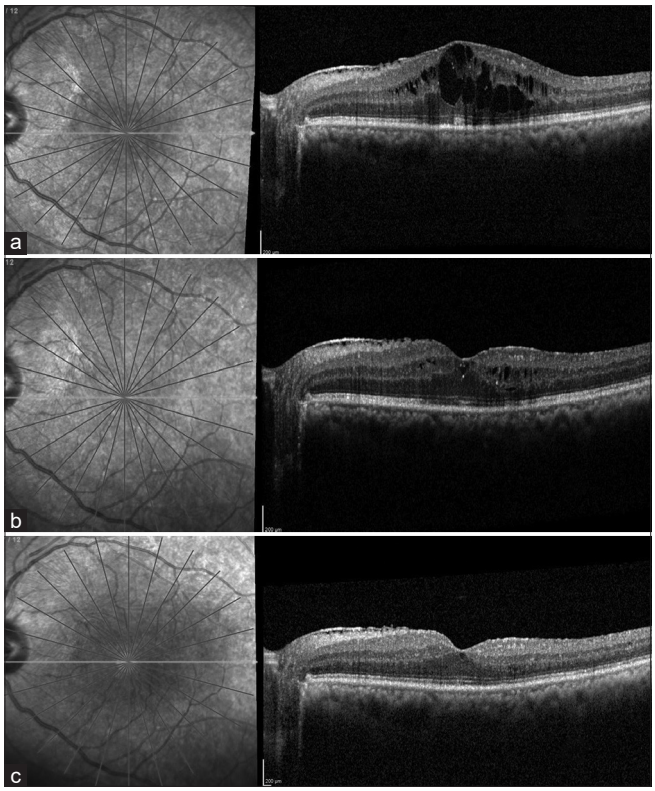

Figure 1: SD-OCT scan of left eye in Case 1 shows cystoid macular edema with epiretinal membrane (a); after a week of topical interferon therapy, there is significant reduction in the macular edema (b); after 3 months while on tapering dose of topical interferon therapy, the macular edema shows near-complete resolution on OCT scan (c)

pandemic lockdown situations and reverted after 4 months. The patient had discontinued IFN therapy. Recurrence of P-CME was noted (CMT: 686 µm). IOP was normal. IFN therapy was resumed, and after a month CMT decreased to 461 µm, but the vision remained status quo due to worsening keratopathy. The patient was lost to follow-up again.

Case 3: A 58-year-old lady presented with P-CME in OD 1 year after her cataract surgery, which was complicated with PCR. BCVA was 20/80 and IOP was normal. Examination showed mild congestion, pigments on endothelium, iris chaffing, 1 + cells and/or pigments in AC, pseudophakia, pigments in the vitreous, and CME. SD-OCT scan showed CMT 454 µm [Fig. 3]. The patient was started on topical dexamethasone (0.1%) eye drops six times/day in tapering dose along with nepafenac (0.1%) eye drops. After 2 weeks, CMT had increased to 563 µm. Topical IFN therapy was started after patient's consent, and dexamethasone was further tapered while nepafenac was continued. The patient was lost to follow-up due to COVID-19 pandemic lockdown and returned after 2 months. The patient had used IFN drops for 2 weeks and stopped all medications. Repeat SD-OCT scan showed complete resolution of CME, rest ocular examination was normal. Vision improved to 6/9 and IOP remained normal.

Case 4: A 64-year-old man presented with P-CME 5 months post traumatic cataract surgery and posterior iris claw lens and vitrectomy in OS. The patient was treated with IVTA 1½ months ago and was advised another injection of IVTA due to worsening CME. IOP was 20 mmHg with brinzolamide (1%) + brimonidine (0.2%) and timolol (0.5%). Examination

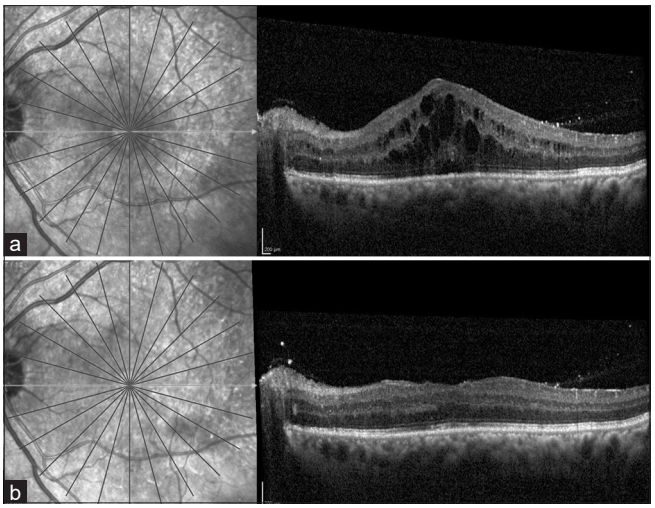

Figure 2: SD-OCT scan of the left eye in Case 2 shows cystoids macular edema with mild subretinal fluid (a), after a month of topical interferon therapy, there was complete resolution of the macular edema (b)

showed pigment dispersion in AC and in the vitreous. Fundus examination was normal except CME (CMT: 702 µm). IFN monotherapy was commenced after the consent. SD-OCT scan after 2 weeks showed dramatic reduction of CMT (400 µm). After a month, CME resolved and IOP remained under control (12 mmHg) with the above medications. CDVA improved to 20/30. IFN was tapered to TID dose, but the patient discontinued it after a month along with other antiglaucoma medications and came back after 20 days with recurrence of CME (CMT: 900 µm). QID dose of IFN was resumed, and only timolol was restarted as the IOP was 16 mmHg. The patient is under follow-up.

Case 5: A 50-year-old man had undergone cataract surgery 8 years ago, developed retinal detachment, and underwent two surgeries (vitrectomy) in OS for the same 1 year ago. The patient developed P-CME and received anti-VEGF (bevacizumab, single injection) and subsequently IVTA for the recurring CME 2 months prior to presentation. CME had resolved 1 month post IVTA injection, but the patient was found to be a steroid responder and was put on dorzolamide (2%) + timolol (0.5%). At presentation, his CDVA was 20/80 in OS and IOP was 17 mmHg. Examination showed 0.5 AC cells or pigments, pseudophakia with PCR, and attached retina post silicone oil removal. OCT revealed recurring macular edema [Fig. 4a]. IFN monotherapy trial was commenced after the consent, and 3 months later OCT showed near-complete resolution of CME [Fig. 4b]. CDVA improved to 20/60. IOP remained under control with above medications. The patient is still under follow-up.

Case 6: A 67-year-old man with a history of cataract surgery in OD 25 years back had undergone YAG (yttrium aluminum garnet) capsulotomy 5 months ago. The patient presented with complaints of blurring of vision in OD. Examination showed pigments on the back of cornea, pseudophakia with PCR, and normal fundus examination except CME. SD-OCT scan revealed CMT 478 µm. The patient consented to topical IFN therapy, and after a month CME resolved. Further, the patient was lost to follow-up, stopped the drug, and reverted after 2.5 months. No recurrence of CME was seen.

Case 7: A 48-year-old man known case of Fuchs' uveitis had undergone cataract surgery in OS 8 years ago, presented with complaints of blurring of vision. CDVA in OS was 6/36. Examination showed typical Fuchs uveitis findings (diffuse microgranulomatous keratic precipitates [KPs], AC

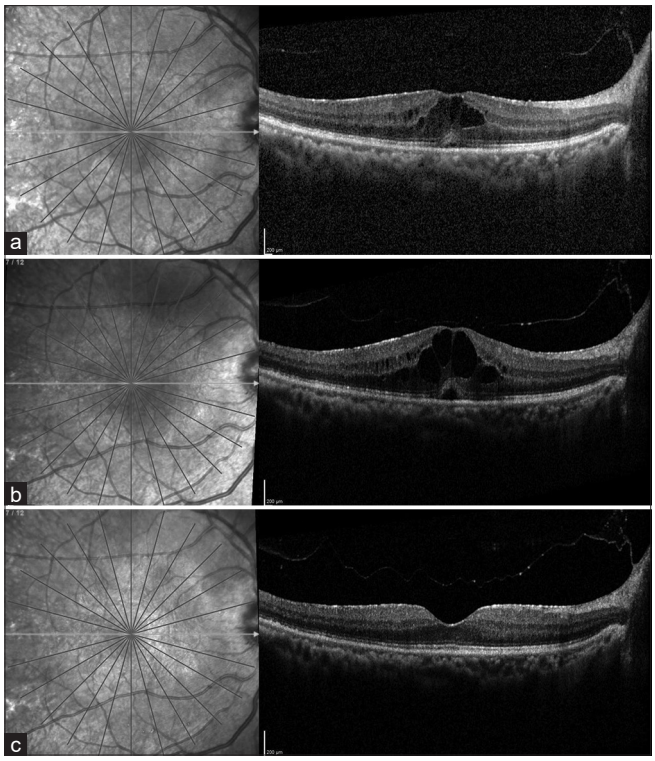

Figure 3: SD-OCT scan of the right eye in Case 3 shows cystoid macular edema (a); after 2 weeks of topical steroid and nonsteroidal therapy, macular edema increased (b); after starting topical interferon therapy, repeated scan after 2 months shows complete resolution of the edema (c)

cells 1+, altered iris pattern, vitritis 1+, and posterior vitreous detachment), PCIOL (posterior chamber intraocular lens) with PCR, and normal fundus except CME (CMT: 585 μm). The patient consented for topical IFN therapy, and after 2 weeks CMT decreased to 501 μm and resolved after 6 weeks. But the patient developed papillary conjunctivitis, which was managed with topical fluoromethalone. Partial resolution of KPs was also noted. Furthermore, IFN was tapered to TID dose. The patient is under follow-up.

Case 8: A 62-year-old lady underwent uncomplicated cataract surgery with PCIOL implantation and was diagnosed as P-CME after 3 months. The patient was started on topical prednisolone (1%) eight times/day with topical nepafenac (0.1%) TID for a week, but CMT increased from 407 μm to 477 μm. Her CDVA was 6/9, and IOP was 12 mmHg. Topical prednisolone and nepafenac were discontinued, and she was switched over to IFN monotherapy in QID dose after the consent. First follow-up SD-OCT scan was done after 7 weeks and showed complete resolution of CME. IFN dose was tapered to TID and had to continue for 6 months as there were two recurrences in the form of a single small cyst (100 μm) that resolved with the continuation of IFN in TID dose. The patient is under follow-up.

Discussion

In the present series, we evaluated the role of topical IFN therapy in P-CME. The preparation of the drug and dose of IFN therapy was based on previous publication by Maleki *et al*.[5] All eyes except one (Case 8) in our study had a PCR. Good therapeutic response was seen at 2 weeks follow-up. CMT decreased significantly within 1 to 2 weeks in most of the cases [Table 1]. In Case 5, near-complete resolution was observed only after 3 months as the patient could not adhere to

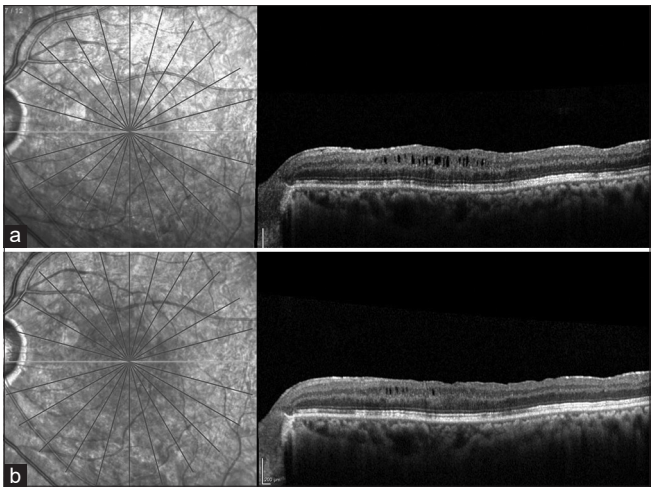

Figure 4: SD-OCT scan of the left eye in Case 5 shows multiple cystoid spaces (a), near-complete resolution is seen after 3 months (b)

the recommended QID dose in the first month of the therapy. In Case 1, during the initial 2 weeks of IFN therapy, the patient was also on bromfenac eye drops. But bromfenac perhaps had little role to play as the patient was using it even before the recurrence of CME. This patient had received IVTA 3 months before the IFN trial. Considering the shorter washout period (<3 months) of IVTA in vitrectomized eyes, and considering the recurrence 3 months after IVTA that resolved after starting the IFN drops, the role of IFN in resolution of CME was clear in this case. Inspired from Case 1, topical "IFN monotherapy" was commenced as the primary treatment in Case 2, which also showed good response. The response to IFN was consolidated when inadvertent discontinuation of the drug resulted in recurrence, and resumption showed improvement. In Case 3, although the patient used the drug only for 2 weeks and stopped, follow-up at 2 months did not show recurrence. Topical steroid and nepafenac drops were deemed failed in this case, as the CME increased after 2 weeks of their use and the same was true for Case 8. Cases 4 and 5 are good examples of how steroid responders can be safely treated with topical IFN. Case 6 is a rare case of post–YAG capsulotomy occurrence of P-CME. In this case also no recurrence was noted after 2.5 months of inadvertently stopping IFN therapy. Case 7 is yet another rare case of Fuchs uveitis developing CME after 8 years of cataract surgery. In addition to CME improvement, partial resolution of KPs was also noted. No ocular or systemic side effects related to IFN were observed clinically in any patient except Case 7 who developed papillary conjunctivitis. With the above case examples, we have shown that the topical IFN is useful in the treatment of P-CME and may have prospect in the treatment of uveitic CME as well.

IFNs were discovered as antiviral agents but also found useful in several inflammatory conditions.[10] Systemic IFN is widely used in uveitic conditions such as Behcet's disease, multiple sclerosis, and other sight-threatening uveitis refractory to conventional immunosuppressive therapy.[6-8] Subcutaneous IFN has shown promising results in the treatment of resistant uveitic macular edema.[9] Subcutaneous IFN has also been used in P-CME.[11] Side effects such as fatigue, flu-like symptoms, as well as IFN-induced retinopathy due to systemic administration of the drug have been reported.[12,13] Invasive procedure and the cost of the drug in recommended doses[11] are major limiting factors for its systemic use, whereas the safety of topical IFN is well proven. Minor side effects such

as conjunctival hyperemia, papillary conjunctivitis, corneal epithelial defect, superficial keratitis, and very rarely flu-like symptoms that resolve after discontinuation of IFN have been reported.[14] But no significant side effects were observed in a recent randomized controlled trial of 50 patients.[4] In our series, only one case developed papillary conjunctivitis after 1 month. Longer follow-up may be needed to assess the side effects and their recurrence or persistence.

Maleki *et al*.[5] noted significant improvement after 1 month with QID dose and 3 months for complete resolution. In contrast to their report, dramatic improvement was noted within 1 to 2 weeks in most of our cases, and complete resolution was noted in five cases within 1 to 2 months [Table 1]. All our cases except Case 8 had a PCR. Unfortunately, SD-OCT scan was not available at 2 and 4 weeks in this patient to comment on the speed of recovery. The presence of PCR perhaps facilitated the penetration of the drug in the posterior segment in our cases. Studies are needed to evaluate the posterior segment penetration of topical IFN before considering intravitreal administration of IFN as reported previously for age-related macular degeneration.[15] Long-term follow-up after starting IFN therapy (≥6 months) was available only in three patients. Three had recurrence: Cases 2 and 4, due to inadvertently discontinuing the therapy by the patients, and Case 8, due to unknown cause. The recurrence in Case 8 was negligible, which resolved with the continuation of the same dose of IFN. The possibility of missing out few doses before the relapses cannot be ruled out in this patient. Due to lack of long-term follow-up, recommendations for the exact duration of IFN therapy cannot be given from this study. But considering Case 1 who had 9 months post treatment follow-up and Case 8 having 8 months of follow-up with two minor recurrences, we propose QID dosing until first complete resolution and thereafter tapering 1 drop per month unless there are signs of recurrences on SD-OCT scan.

Inhibition of inflammasome activation, reduction of TNF-α, and interleukin (IL)-6 secretion can explain the anti-inflammatory effect of IFN especially for IFN-β, which are considered predominantly anti-inflammatory.[16-18] Downregulation of VEGF gene expression, inhibition of basic fibroblast growth factor, IL-8, and restoration of blood–retinal barrier could be the possible underlying mechanisms of action of IFN in the resolution of CME.[4,19-21]

The recommended dosing for subcutaneous IFN alfa-2a (Roferon-A®, Roche) injection for P-CME is significantly higher.[11] With the QID dosing, 3 mL reconstituted IFN alfa-2b (Intalfa(R), Intas) drops in our patients lasted approximately for 2 weeks, incurring the cost of the treatment around 1,600 INR (15 USD) for a month. Thus, topical IFN therapy is not only safer, convenient, and self-administrable but also economical alternative compared with its systemic use and anti-VEGF medications when they are given multiple times.

Our study is limited by the smaller number of cases and short follow-up, and also lacks control arm. But our case series confirms the role of topical IFN in P-CME as observed in the previously published single case report. Our study also suggests that posterior capsular opening may enhance the penetration of the drug into the posterior chamber. In addition, it also instigates evaluation of its use in different uveitic conditions.

Conclusion

To the best of our knowledge this is the first case series in the literature of P-CME, which effectively documented resolution of the CME with "topical IFN-only" therapy and also showed a faster resolution in the presence of PCR. Larger randomized controlled trials are needed to further investigate and validate the role of topical IFN therapy in P-CME as well as in uveitis.

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Conflicts of interest

There are no conflicts of interest.

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