Purpose: To evaluate the efficacy of intensive topical interferon alfa-2b (IFN) therapy in uveitic macular edema (UME). Methods: This is a prospective, interventional case study of eyes with UME. Commercially available injection IFN for subcutaneous use was reconstituted to form eye drops and a dose of 6 times/day for 2 weeks, 5 times/day for next 2 weeks, followed by 4, 3, 2, 1 taper per month was prescribed. Optical coherence tomography (OCT) and clinical examination was done at 0, 2, 4, 8 weeks, and further as required.

Results: Nine eyes of 9 patients with UME were studied. Mean central macular thickness (CMT) at presentation was 522.2 µm (range: 408–803 µm). At 2-week, 1-month, and 2-month follow-up, mean CMT decreased to 451.6 µm (range: 322–524 µm), 375.8 µm (range: 287–480 µm), and 360.3 µm (range: 260–485 µm), respectively. Four eyes which showed inadequate response to previous topical IFN therapy (4 times/day) showed significant improvement with intensive therapy at 1 month follow-up. In 4 eyes, UME resolved completely with mean CMT 285.5 µm (range: 260–312 µm) at 7.5 weeks (range: 4–12 weeks). Study exit was seen in 2 cases due to inadequate response and relapse of uveitis. Mean follow up was 3.38 months (range: 1–5 months). Conclusion: Intensive topical IFN therapy can be an alternative therapeutic option in the treatment of UME. Study of intraocular penetration, combination with other drugs, and the efficacy of IFN separately for different uveitic entities may explore new avenues in treatment of UME.

Key words: CME, eye drops, intensive therapy, interferon, macular edema, topical, uveitic macular edema

Uveitic macular edema (UME) occurs in 8.3% of non-infectious uveitis patients and can persist without any sign of concurrent inflammation. Conventional treatment involves the use of steroids via various routes. Topical non-steroidal anti-inflammatory drugs (NSAIDs), anti-vascular growth factor (anti-VEGF), immunomodulatory agents and biologics have been used in the treatment of UME. The very first use of topical interferon alfa-2b (IFN) therapy in the treatment of pseudophakic macular edema was done by Maleki et al. Subsequently a case report and a small series supported its role in pseudophakic and in post-endophthalmitis cystoid macular edema (CME). A randomized controlled trial (RCT) has also demonstrated the safety and beneficial effect of topical IFN in diabetic macular edema (DME), although statistically insignificant. DME may differ from UME. Hyperglycemic mediated formation and accumulation of advanced glycation end products, leading to an abnormally adherent vitreoretinal interface, and further breakdown of blood retinal barrier can be responsible for the DME. UME is due to breakdown of the blood retinal barrier mainly formed of tight junctions between endothelial cells and retinal pigment epithelial (RPE) cells, which in turn could be due to various inflammatory factors like, VEGF and pro-inflammatory cytokines: IL-6, IL-8, TNF-α, IL-1, TGF-β, angiotensin II, adenosine, histamine, and metalloproteinases. These factors also play a role in development of DME as well. Spectral domain optical coherence tomographic (SD-OCT) characteristics of UME may also differ from DME. It may show fluid accumulation either at the inner or outer plexiform layer and between retinal septa, typically producing a cystoid shape.

In this study, we investigated the role of intensive topical IFN therapy in the treatment of UME.

Methods

This is a prospective, interventional, longitudinal case 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 the Declaration of Helsinki.

Inclusion criteria

- Patients diagnosed with UME and advised for intensive topical, systemic, periorcular or intraocular injection of steroids or intravitreal injection of 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 SD-OCT scan after 3–4 weeks of the previous treatment.
- Patients not showing improvement of at least 50 µm in UME on the SD-OCT scan in 3–4 weeks of topical IFN therapy in 4 times/day dose.

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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.
• Patients with macular edema due to overlapping pathology other than uveitis (e.g., diabetic macular edema).
• Patients with follow-up of less than one month.

Patients fulfilling the above-mentioned criteria were offered an alternative therapeutic option of “intensive topical IFN therapy.” Patients who consented were enrolled into the study. Patients who did not show any improvement in UME after a month or patients with relapsing uveitis during follow-up which needed increase in IMT and steroids, or patients who opted for conventional treatment during the follow-up exited the study.

IFN eye drops were prepared from commercially available subcutaneous prefilled injection IFN 3 MU/ml (Inj. Intalfa™). The drug was diluted using 2 ml of sterile water for injection to constitute 3 ml IFN (1 MU/ml) eye drop solution.[9] Patients were handed over the freshly prepared IFN eye drops (every 2 weeks) in an ice pack with the instruction of storage in the refrigerator door at 4°C and were started on intensive topical IFN therapy. The dosing of intensive topical IFN therapy was as follows: 1 drop 6 times/day for 2 weeks, 5 times/day for next 2 weeks, then 4 times/day until the resolution of UME, followed by tapering of 1 drop per month.

Patients, who were already on oral and topical steroids were tapered further after commencing IFN therapy by 10 mg per week or 1 drop per week, respectively, and stopped. Topical NSAIDs were discontinued after witnessing first improvement on SD-OCT scan within a month. IMT was continued in same dose if the patients were already on (IMT) [Table 1].

Corrected distant visual acuity (CDVA), intraocular pressure (IOP), slit-lamp biomicroscopy, indirect ophthalmoscopy, and SD-OCT scan were done at the baseline, at 2 weeks, 4 weeks and 8 weeks and further when needed. The study outcome was measured as an increase or decrease in CMT after IFN therapy. CMT was noted as on thickness map using Heidelberg™ OCT software [Table 2].

Statistical analysis: All data was entered using Microsoft Excel 365 and analyzed using IBM SPSS version 27.0 for windows. Comparison of means was done using the paired samples t test and a P value of less than 0.05 was considered significant.

Results

Nine eyes of nine patients were included in the study. The mean age of presentation was 48.1 years (range: 31–74 years). Four were male and five were females. Four patients showed increase or no improvement more than 50 µm in CMT after 1 month of IFN in QID dose [Table 2]. Previous medications and medications at the enrollment were as shown in Table 1. Two patients were known steroid responders. Mean IOP at the enrollment and at the final visit was 13 mmHg (range: 11–18 mmHg and 9–20 mmHg, respectively). Four eyes were pseudophakic and none had posterior capsular rent.

Mean CMT at the enrollment was 522.2 µm (range: 408–803 µm) which improved to 451.6 µm (range: 322–524 µm) at 2-week follow-up. At 1-month follow-up, mean CMT was 375.8 µm (range: 287–480 µm) (n=6). At 2-month follow-up, mean}

| Cases | Medications at the time of the enrollment, with duration | Medications received and discontinued during 3 months, before the enrollment, with duration |
|-------|----------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 1     | IFN 4 t/d, 8 weeks                                       | Bromfenac e/d, 2 months                                                                       |
|       |                                                           | T. Prednisolone, 2 months                                                                     |
|       |                                                           | Brimonidine + Timolol, 1 ½ months                                                             |
| 2     | IFN 4 t/d, 4 weeks                                       | Prednisolone e/d, 1 month                                                                     |
| 3     | Nepafenac e/d, 4 weeks                                   | T. Deflazacort, 2 months                                                                      |
| 4     | ATT, 2 months                                            | Nepafenac, 1 week                                                                             |
| 5     | IFN 4 t/d, 3 weeks                                       | Prednisolone e/d, 1 month                                                                     |
| 6     | Prednisolon e/d, 3 weeks                                 | Nil                                                                                            |
| 7     | T. Prednisolone 30 mg taper, 2 weeks                     | Nil                                                                                            |
| 8     | Nil                                                      | Prednisolone e/d, 2 months                                                                    |
| 9     | Nepafenac, MTx 20 mg, 5 months + AZA 50 mg, 4 months    | T. Prednisolone, 3 months                                                                     |

IFN: interferon, t/d: times per day, e/d: eye drops, ATT: Anti tubercular treatment, MTx: Methotrexate, AZA: Azathioprine

CMT improved to 360.3 µm (range: 260–485 µm) (P = 0.016). In four eyes, UME resolved completely with mean CMT 285.5 µm (range: 260–312 µm) at 7.5 weeks (range: 4–12 weeks). Study exit was seen in two cases due to inadequate response (case 3), relapse of uveitis (case 9) and one patient (case 7) was lost to follow-up after 2 months. Mean follow up after starting topical IFN 6 times/day was 3.38 months (range: 1–5 months).

Out of four patients with successful resolution of UME, two (cases 1 and 2) were previously on IFN therapy initiated with QID dose. In case 1, after use of IFN in QID dose for 8 weeks, CMT had worsened by 60 µm and in case 2, after use of IFN in QID dose for 4 weeks, CMT improved only by 20 µm. Significant improvement with intensive therapy was seen in both the cases [Table 2].

Mean corrected distant visual acuity (CDVA) at the enrollment was 20/50 (range: 20/20–20/125) and mean CDVA at final follow-up was 20/40 (range: 20/20–20/80). No ocular or systemic side effects were seen. Only in case 1 did IOP increase to 40 mmHg, 1½ months after the enrollment. The patient was a known case of steroid-induced glaucoma, had undergone trabeculectomy 14 months before, and was off anti-glaucoma medications for 1½ months before the enrollment. He had discontinued steroids 2 months before the enrollment. He was put on T. acetazolamide 250 mg 3 times/day for 3 days to achieve immediate IOP control, along with topical brinzolamide (1%) 3 times/day, brimonidine (1%) + timolol (0.5%) 2 times/day, and after a month, latanoprost (0.005%) once a day was added. IFN was tapered as per the treatment protocol. No recurrence of UME was seen and the IOP came under control. Relapse of UME was seen in one patient with retinal vasculitis (case 3) after 3 months of the therapy and exited from the study.
Table 2: Diagnosis and therapeutic response

| Cases | Diagnosis                                  | IFN 4 times/day | Change in CMT | Intensive IFN therapy OCT follow-up |
|-------|--------------------------------------------|-----------------|---------------|-------------------------------------|
|       |                                            | Duration (weeks) | CMT 0 day     | CMT 2 weeks | CMT 1 Mon | CMT 2 months |
| 1     | Panuveitis- Presumed TB                    | 8               | +60           | 408        | 350       | 335         | 312         |
| 2     | B/L Alternating N G Ant Uveitis            | 4               | –20           | 556        | 524       | 287         | 260         |
| 3     | Vasculitis                                 | 5               | +30           | 562        | 524       | 480         | 485         |
| 4     | Panuveitis with vasculitis- presumed TB    | NA              | NA            | 443        | 322       | 306         | 306         |
| 5     | Kerato-uveitis (IU)                        | 3               | +36           | 435        | 418       | 374         | 351         |
| 6     | N G Ant Uveitis                            | NA              | NA            | 803        | 472       | NA          | 264         |
| 7     | VKH                                        | NA              | NA            | 528        | 484       | 459         | 404         |
| 8     | Resolved CMV-R                             | NA              | NA            | 519        | 519       | 390         | 488         |
| 9     | Panuveitis- presumed sarcoid               | NA              | NA            | 446        | NA        | NA          | 373         |

TB: Tuberculosis, B/L: Bilateral, N G: Non-granulomatous, IFN: interferon, t/d: times per day, IU: Intermediate uveitis, VKH: Vogt Koyanagi Harada, CMV-R: Cytomegalovirus retinitis, N.A.: Not applicable/Not available, CMT: Central macular thickness, e/d: eye drops

Discussion

We evaluated efficacy of intensive topical IFN therapy for UME in various types of anterior, posterior, and panuveitis [Table 2]. All our cases had UME but no other clinically evident inflammatory signs that warranted increase in steroids or IMT at the enrollment. We also included cases where UME was worsening with previous medications, which suggested inadequate response to the previous medications. After commencing intensive IFN therapy, IMT was continued in same doses, steroids were tapered further and stopped, and NSAIDs were discontinued after witnessing first improvement. This allowed us to assess the efficacy of the intensive IFN therapy with the least treatment biases. Statistically significant improvement was observed at 2-month follow-up in our series (P = 0.016).

The efficacy of topical IFN therapy in QID doses was proven in previous reports for pseudophakic macular edema, post-endophthalmitis macular edema, as well as diabetic macular edema.[2–5] Four cases in our series were on IFN QID doses showing inadequate response. After commencement of intensive topical IFN therapy, improvement in UME was noted at 1 month follow-up. At 2 months, the improvement was significant and in two cases, UME resolved completely. Out of other five patients with no prior history of topical IFN therapy (cases 4, 6, 7, 8, 9), two showed (cases 4 and 6) resolution and two showed (cases 7 and 9) improvement of more than 50 µm at 2-month follow-up. This suggests that intensive topical IFN therapy may have a role in the treatment of UME.

Pseudophakic status and posterior capsular opening has been hypothetically related to IFN drug penetration in the posterior segment.[3] In our series, only four eyes had pseudophakia without posterior capsular breach. Significant improvement at 1 month and resolution in two cases with phakic eyes suggests penetration of IFN in therapeutic concentration in the posterior segment with intensive therapy.

Case 3, which did not show adequate response to the intensive therapy, was a case of occlusive vasculitis. We believe the subclinical inflammation outbalanced the therapeutic effect of topical IFN in this case. Another patient with inadequate response was case 8 with a history of resolved cytomegalovirus retinitis with UME who also had undergone retinal detachment surgery with silicon oil implantation. The role of intravitreal or posterior sub-Tenon’s injection of IFN in such cases remains to be investigated. Intravitreal use of IFN has been done in the past, in cases of DME and age-related macular degeneration.[9–11] But a case of IFN-induced retinopathy post perilesional injection for ocular surface squamous cell carcinoma has also been reported raising concerns over its intravitreal use.[12] In contrast, subconjunctival IFN injection for pseudophakic macular edema has not shown any side effects.[13] Although no ocular or systemic side effects were seen in this series, which can be directly linked to the IFN therapy, in case 1, we were unable to explain a sudden increase in IOP after 1½ month of IFN therapy. Such unexplained raise in IOP has also been reported for systemic IFN therapy by Kwon et al.[14] In contrast, IOP-lowering effect was reported in a randomized controlled trial of topical interferon therapy for DME.[15] Systemic IFN-associated presumed ocular sarcoidosis has also been reported.[15] In one of our patients (case 9) with the diagnosis of presumed sarcoid-panuveitis, recurrence of anterior uveitis was seen after 2 months of IFN therapy, although there was improvement in the UME [Table 2]. It is debatable whether IFN induces or causes relapses in sarcoid-uveitis.

Exact mechanism of action as well as the drug penetration of topical IFN in posterior segment and the resolution of macular edema is not well studied. Restoration of interleukin (IL)-2 production, reduction of TNF-α, IL-6, and inhibition of inflamasome activation can explain its anti-inflammatory effect.[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.[19–21] It’s action on NK cells, CD8 T cells, and CD3 T cells may also have an anti-inflammatory role.[22]

The dose of subcutaneous IFN therapy for pseudophakic CME, uveitic CME, and post-CMV retinitis CME is significantly higher,[23,24] and hence the cost. With our dosing protocol, the cost of topical IFN therapy per month was around 2,520 INR (33.2 USD). Considering the minimum 3 months of therapy with topical IFN, the cost effectiveness is lower when compared to other conventional topical medications. But topical IFN could be an economical alternative compared to intravitreal anti-VEGF medications or steroid implants when they are given multiple times.
The limitation of this study are small numbers, uncontrolled design, inclusion of different types of uveitis, and a short follow-up. The other limitation was inability to estimate drug penetration into the eye as also acknowledged by Afarid et al. in their randomized controlled trial. Patient’s compliance and inappropriate storage of the medication are also factors to be considered into the limitation of the study.

Conclusion

Our study is the first to evaluate outcomes of intensive topical IFN therapy for UME. Our study suggests that UME may need increased dosing of topical IFN compared to previously reported dosing for pseudophakic macular edema. Study of its intraocular penetration, efficacy in combination with other drugs, and its evaluation separately for different uveitic entities may explore new avenues in treatment of UME.

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Conflicts of interest

There are no conflicts of interest.

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