

Commentary: Topical interferon: A novel approach to uveitic macula edema

Uveitic macula edema is the most common cause of visual impairment in patients with uveitis. It accounts for 8.3% of noninfectious uveitis.^[1] This sequela of uveitis is a challenging complication that requires aggressive therapy with periocular or intravitreal steroids, systemic steroids, and immunosuppressive drugs.^[2] Response to this conventional treatment is good when the treatment is associated with active inflammation. In the absence of active inflammation, response to treatment may be inadequate.^[3] Hence, an alternate or new treatment options needs to be evaluated for refractory uveitic macula edema [Table 1].

Interferons were first discovered as antiviral agents. They are intracellular cytokines that play an important role in the regulation of both innate and adaptive immunity but also help in the treatment of several systemic autoimmune

diseases. Interferon alpha-2a and interferon alpha-2b subtypes were first described as treatment options for uveitis refractory to conventional treatment in cases of ocular Behçet's disease. In Behçet's disease, multiple sclerosis, and other sight-threatening uveitis refractory to conventional immunosuppressive therapy, interferon therapy has proven to be beneficial. Inhibition of inflammasome activation, reduction of tumor necrosis factor alpha (TNF- α) and interleukin (IL)-6 secretion explains the anti-inflammatory effect of interferon. 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 interferon in the resolution of uveitic macula edema.^[4]

In the contemporary time, interferon alpha-2a is known to be superior to the conventional treatment in Behçet's disease due to the rapid onset of action and lesser chances of recurrences following remission.^[5] There are additional reports of uveitic macula edema in Behçet's disease which regressed within

Table 1: Studies on topical interferon therapy in uveitic macula edema

Author	Design of the Study	Results
Kawali <i>et al.</i> ^[14]	Prospective, interventional case study of eyes with uveitic macula edema.	Topical interferon therapy showed resolution of macula edema. It can be an alternate treatment option in eyes with uveitic macula edema.
Kawali <i>et al.</i> ^[10]	Case report on macula edema following post-traumatic endophthalmitis.	Steroid response and patient's reluctance to injections, topical interferon therapy was opted. Macula edema resolved in 2 months.
Maleki <i>et al.</i> ^[15]	Case report on efficacy and safety of interferon alpha-2b in the treatment of pseudophakic cystoid macular edema resistant to conventional therapy.	Topical interferon alpha-2b is safe and effective treatment option of refractory cystoid macular edema after cataract surgery.
Deuter <i>et al.</i> ^[3]	A prospective pilot study to evaluate interferon alpha-2a for the treatment of refractory cystoid macular edema in endogenous uveitis.	Topical interferon is an effective treatment option of refractory uveitic macular edema.

four weeks of the initial interferon treatment.^[6,7] Additional complications such as steroid-induced glaucoma, cataract, central serous chorioretinopathy, and worsening of infections in uveitis cases can be avoided with the use of topical interferons.

Therefore, a recent prospective study evaluated the efficacy of topical interferon therapy in uveitic macula edema. They concluded that topical interferon therapy in uveitic macula edema is safe and long-term therapy is needed to improve its efficacy.^[8]

Interferon alpha-2b has poor stability and undergoes degradation under thermal stress and in acidic or basic pH. Storing it in the refrigerator, using ice packs during transportation, and preparing it with distilled water (for maintaining neutral pH) decreases chances of degradation of the drug.

Another concern is that of adequate penetration to the posterior vitreous and retina via topical administration. Lincoff *et al.*^[9] demonstrated high concentration of interferon alpha in the choroid after retrobulbar injection. Also, the efficacy of interferon alpha-2b via sub-Tenon's administration has been reported in the treatment of diabetic macular edema, indicating good penetration of the drug into sclera despite its high molecular weight. However, animal studies are needed to investigate the pharmacokinetic and pharmacodynamic properties of topical interferon therapy.

In pseudophakic cystoid macula edema, 3 ml of reconstituted interferon alpha-2b was instilled four times per day for two weeks. This QID dose has also been effective in post-endophthalmitis macula edema and diabetic macula edema.^[10,11] It not only proved to be effective but was also cost effective. Thus, considering the total duration of topical interferon therapy for approximately three months, topical

interferon therapy is safe, convenient, and self-administrable. It is also an economical alternative compared with its systemic use and anti-VEGF medications which require multiple injections.^[12]

A prospective pilot study evaluated the efficacy of topical interferon for resistant uveitic macula edema. Eleven eyes responded well to treatment and edema resolved completely with six months of treatment.^[2]

Kawali *et al.* reported on the effective treatment of inflammatory macula edema using topical interferon therapy. In such a scenario where steroids or intravitreal anti-VEGF may aggravate the inflammation, topical interferon therapy will be beneficial.^[10,13]

Adverse effects such as fatigue, flu-like symptoms and interferon-induced retinopathy due to systemic administration of the drug have been reported. Cost of the drug is a major limiting factor in the systemic use of the drug. The safety of topical interferon is well proven, but 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 interferon therapy have been reported.^[2,11,16] But no significant side effects were noted in a recent randomized control trial with 50 patients.^[13]

Thus, topical interferon therapy may be beneficial for patients with refractory uveitic macula edema when the conventional treatment fails. However more studies are needed to evaluate the mechanism of topical interferon therapy and the optimal dosing schedule in uveitic macula edema. Also, its efficacy in combination with other drugs and for each uveitic entity is required.

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