Review Article

ROLE OF INTERFERONS IN OCULAR DISEASES AND THEIR ADVERSE EFFECTS: A REVIEW

Parul Singh¹, Abhishek Singh²

 ¹ Department of Ophthalmology, Veer Chandra Singh Garhwali Government Medical Science and Research Institute, Srinagar Garhwal, Uttarakhand, India.
²Department of Radiotherapy and Clinical Oncology, Veer Chandra Singh Garhwali Government Medical Science and Research Institute, Srinagar Garhwal, Uttarakhand, India.

ABSTRACT

Interferons are natural glycoproteins that have anti-viral, anti-proliferative and immune regulatory functions. They are classified into interferon- alpha, beta and gamma. They have proven role and are used in treatment of various cancers, hepatitis-C and immune mediated conditions such as multiple sclerosis. Beneficial effects of interferons in ocular diseases such as Behcet's disease, multiple sclerosis associated uveitis, intra-ocular inflammation and chronic macular edema has been documented. It also has been found useful topically as an adjuvant treatment in viral keratitis and ocular surface malignancies. Thus, interferons are gaining a place in the treatment of ocular diseases. This article provides insight into role of interferons in ocular diseases and their potential adverse effects.

Key words: Interferons, Ocular diseases, Eye, Side effects, leukemia, lymphoma.

INTRODUCTION:

Interferons (IFNs) were discovered in 1957 [1] as natural anti-viral substances produced during viral infection and were characterized for their ability to interfere with viral replication, reduced cell proliferation and alter immunity. Interferon beta-1a and interferon beta-1b are used to treat and control multiple sclerosis, an auto-immune disorder. Interferon therapy is used in combination with chemotherapy and radiation therapy as treatment modality for many cancers [2] such as leukemias and lymphomas including hairy cell leukemia, chronic myeloid leukemia, nodular lymphoma, cutaneous T-cell

lymphoma. Both hepatitis-B and hepatitis-C are treated with interferon alpha often in combination with other antiviral drugs [3,4]. Intereferon-a2b is also been used for treatment of ocular surface neoplasia in form of peri-lesional injection followed by topical interferona2b drops. Other ocular uses of interferons are in treatment of viral keratitis, conjunctivitis, Mooren's ulcer and advanced neovascular age related macular diseases (ARMD). When used systemically, they have a role in patients with multiple sclerosis or optic neuritis, uveitis in patients of Behcet's disease and uveitis related cystoid macular edema. They can be used to prevent and

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treat viral respiratory diseases such as cold and flu. In this article, we review the current knowledge of interferons in immunity, auto-immunity and their use in clinical ophthalmological practice and their potential adverse effects.

Types:Based on amino acid composition and biological properties, interferons have been classified as Type I and II. Type I includes at least thirteen different isotypes of interferon alpha and single interferon beta. Both of these bind to common receptor IFN-alpha/beta. Type II includes a single member IFN gamma which binds to receptor IFNGR.

Role of interferons in immunity: Interferons are synthesized and secreted monocytes, macrophages, bv Т lymphocytes, neurons and glial cells. Early viral infection leads to stimulation of plasmacytoid dendritic cells, the main producers of IFN-I and subsequently IFN gamma. This leads to induction and maintenance of T-helper type I cells, CD₈, cytotoxic T cells, and natural killer cells. The interferons also have antiproliferative and pro-apoptotic effect on T cells, development of tolerance promoting regulatory T cells, positive as well as inhibitory effect on B cell development and survival.

Role of interferons in autoimmunity: The role of interferons in auto-immunity has been implicated in systemic lupus erythmatosis (SLE), diabetes mellitus, uveitis, multiple sclerosis, sarcoidosis including sarcoidosis associated uveitis [5].

Local use in ocular diseases:

Ocular surface neoplasia: Interferons have been shown to be effective in management of small primary and recurrent corneal and conjunctivalneoplasias in a dose of 1-1.5 million IU/ml, 4-5 times a day topically. IFN a2b has been observed to reduce recurrence rates after primary excision. Similarly, intra-lesional injection of interferon a2b in conjunctival mucosa associated lymphoid tissue lymphoma in a dose of 1.5million IU three times weekly achieved complete clinical and histopathological remission in significant number of cases with very few recurrences [6].

- Mooren's ulcer: Topical IFN α2a as a single therapeutic agent has been reported as an effective alternative in treatment of patients of Mooren's ulcer. It offers the benefits of topical therapy and may avoid surgical intervention in unresponsive cases [7].
- Advanced neo-vascular ARMD: Isolated case reports of intra-vitreal use of single injection of 100000U interferon-a in 0.1ml total volume in patients with advanced neo-vascular ARMD showed a small subjective and objective improvement in visual acuity [8].
- Viral keratitis and conjunctivitis: A combination of topical interferon with topical nucleoside anti-viral agent was observed to significantly improve treatment success.

Systemic use in ocular diseases:

Behcet's disease (BD):Behcet's disease is a multi-system disorder that can affect any organ. Uveitis in a patient with BD is accompanied by severe inflammation with occlusive vasculitis that can lead to visual impairment. Herpes simplex virus type-I is thought to play a role in pathogenesis of BD. Therefore, treatment of BD had introduction of IFN in 1986 for its anti-viral activity. IFN was administered at a dose of 6 million units daily, with dose and frequency

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adjusted depending on clinical response. Subjects showed significant improvement in both visual acuity and posterior uveitis score [10,11,12].

- Multiple sclerosis (MS) associated ** ocular disease: Intermediate uveitis is the most frequent form of MS associated uveitis. Signs of intermediate uveitis are snowbanks, snowballs with continuous retinal peri-phlebitis [13,14]. Secondary changes like formation of cystoid macular edema or occlusive vasculitits can develop, which may be complicated by retinal detachment or vitreous hemorrhage [15]. Macular edema with subsequent epiretinal membrane formation is a challenge and a threat to visual prognosis. Interferon-b has been shown to have beneficial effects in patients with MS or optic neuritis. Patients with initial episode of demyelination and subclinical lesions of MS on MRI brain when treated with weekly intra-muscular injection of 30 microgram of IFN-b1a showed a 50% reduction in progression to clinically definite MS. Also, treatment of uveitis associated with MS, refractory to corticosteroid treatment, with type-I IFN appear to have beneficial effect on visual acuity. intra-ocular inflammation activity, and the presence of cystoid macular edema in a significant number of study subjects. Interferon-b1a and interferon-B1b block interferon-gamma induced disintegration of endothelial junctions and reduce vascular leakage and hence reduce edema od posterior pole [16,17].
- Cystoid macular edema (CME) in uveitis: Macular edema is a major cause of vision loss in patients with uveitis [18]. In patients with inactive uveitis and CME not responsive to systemic steroids and acetazolamide, IFN-a2a has been

shown to be efficacious in a dose of 3-6 million IU daily for 2-4 weeks with complete resolution of CME.

Adverse Effects of Interferons: Most side effects of Type-I common interferons are injection site reaction and flu like symptoms, fever, headache, arthralgia, sweating myalgia, and fatigue. Depression and suicidal intentions can occur during therapy with interferon, independent of pre-existing psychiatric disease. An asymptomatic increase in liver enzymes and a decrease in leucocyte count are seen in some patients. Interferons may also produce ophthalmologic adverse effects. particularly retinal lesions such as cotton woolspots, hemorrhage, microaneurysms and neurovisual impairment. There are of isolated case reports severe ophthlmological complications such as acute exophthalmos, subconjunctival hemorrhage, papilledema, retinal artery occlusion and retinal vein thrombosis.

The real extent of ophthalmological adverse effects caused by interferons unknown. be since mav ophthalmological investigation of these patients appears to be performed only when the patients complained of visual symptoms. In addition to the problem, the underlying disease themselves may cause visual symptoms. also For example, blurred vision could be due to opticalneuritis and diplopia may be related to brainstem lesions in multiple sclerosis [19, 20]. Uveitis and retinal phlebitis have been reported as retinal manifestation of multiple sclerosis [21], and may add to the difficult differential diagnosis of visual disturbances in a patient with multiple sclerosis taking interferon treatment. Thus, the physician may have an impression that the underlying disease is worsening when, in

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fact, the symptoms could be adverse effects of treatment.

Management of IFN therapy: A close collaboration between ophthalmologists and other specialists is helpful to optimally direct IFN treatment. It is necessary to perform extensive clinical examination and have an exact medical history focusing on autoimmune diseases, impaired thyroid or liver function, and previous or current depressive disorders before starting IFN therapy.

CONCLUSION

Interferons seem to be involved in induction of auto-immune disorders as well as their treatment. Interferons have well documented role as immunologic therapy in the treatment of hematologic and solid tumors, viral hepatitis and diseases auto-immune especially multiple sclerosis. In addition, evidence is growing of their role in the treatment diseases, especially of ocular for interferon-a in Behcet's disease and interferon-b in multiple sclerosis intermediate associated uveitis. Although infrequent. but ophthalmological adverse effects related to the use of interferons have been reported. Interferons are used usually in patients of chronic and debilitating diseases and ocular adverse effects may get ignored, eventually affecting their quality of life. Therefore. ophthalmological examination of patients receiving interferon treatment should be done at regular intervals during and after treatment.

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