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Efficacy and safety of topical Interferon Gamma in uveitis cystoids Macular edema treatment

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KEYWORDS

Cystoid macular edema, interferon-gamma, uveitis

A B S T R A C T

Interferons have immunomodulatory effects and are very effective in the treatment of intraocular inflammation. Interferon gamma can also influence fluid transport across RPE. In this pilot study, the efficacy and side effects of topical interferon gamma in ten patients with Cystoid macular edema secondary of uveitis are investigated. One drop of interferon-gamma-IB ampule (containing 10µg/0.05 ^{cc}) was instilled in the eye, once a week for three consecutive weeks. Visual acuity and central macular thickness (measured by OCT) was documented before each eye drop application one week and three months after the last drop. Visual acuity and central macular thickness improved compared to the basic measurements, but the difference was not statistically significant. No ocular side effect was observed.

Introduction

Uveitis is an uncommon condition. However, it occurs among young patients of working age and therefore complications of uveitis have a long-term effect on patients.[1] Cystoid Macular Edema (CME) is the most frequently cited complication of uveitis.[2] Also, chronic CME is the most common cause of moderate vision loss (20/50 – 20/120).[2] The progressive visual loss could be prevented by early diagnosis and treatment.[1,3]

Different medications have been used to treat CME secondary to uveitis including topical, periocular or Intravitreal corticosteroids, oral Acetazolamide, immunomodulatory drugs, Octreotides and Intravitreal injection of Diclofenac or bevacizumab.[4,14] We hypothesized that interferon gamma can reduce Cystoid macular edema secondary to uveitis and therefore increase visual acuity.

Interferons are natural antiviral substances which are able to interfere with viral replication, reduce cell proliferation, and alter immunity. They leave an impact on both innate and adaptive immune responses. Although interferons can induce autoimmune disease, they have been used for the treatment of autoimmune disease. Interferons appear as double agents which are involved in both supportive and suppressive actions. Interferons have two types. Type I includes interferon-x and interferer –β with a common receptor. Type II has only one member, interferon-δ which binds to a different receptor. It has been shown that interferon gamma has receptors on RPE. Miller, Sheldon hypothesize that proper retinal hydration is maintained through a balance of the bimodal functions of interferon gamma on the retinal pigment epithelium[16]. They have evaluated the effect of interferon gamma on the JAK/STAT pathway, a signal transduction pathway represented in human RPE. In this study, we investigated the efficacy and safety of interferon λ in the treatment of Cystoid macular edema secondary to uveitis.

Materials and Methods

In this non-randomized clinical trial, ten patients with Cystoid macular edema secondary to intermediate or posterior or pan uveitis were selected from Uveitis Clinic in Nikookari Eye Hospital, Tabriz, Iran. A full explanation about the study was given to all the patients and an informed consent was obtained from them. All ten patients were older than 18 years old, had intermediate, posterior or pan uveitis at least for three months prior to the study, Cystoid macular edema secondary to uveitis in at least one eye. Their Central Macular Thickness (CMT) > 250 µm was measured by OCT and visual acuities were found to be 20/200 or better.

All the patients were informed that a safe and reliable birth control method needs to be used during the study and six weeks after receiving the last dose of the drop as well. Pregnant and breast feeding patients, ones with a history of ocular herpes simplex, multiple sclerosis, or acute or chronic infectious diseases were not included in the study. In the case of any evidence of infectious disease during the treatment with interferon drops, the patients should be excluded from the study.

Each participant was treated with one drop of interferon gamma-1β ampoule in one of his/her eyes. We used interferon gamma-1b ampoule and the patients received one drop per week for three succeeding weeks. Each drop contained 10 µg per 0.05 ml interferon gamma-1β. All of the participants had Optical Coherence Tomography (OCT) on the first day before instillation of the drops, one week after each drop just before instillation of the next drop, and finally 3 months after the last drop. Visual acuity, intra-ocular pressure (IOP), cell-count in anterior chamber (AC), and cell-count in vitreous were recorded. IOP was measured by means of Applanation tonometer. Intra-ocular inflammation was measured by slit lamp based on the SUN working group grading criteria.

Statistical analysis

The obtained data was analyzed through SPSS 16. Repeated measures of ANOVA were used to compare the quantities at different time intervals. $P< 0.05$ was considered statistically significant

Results and Discussion

In this study, ten patients (three male and seven female) with CME secondary to uveitis were investigated. The mean age of

the patients was 40.20±10.86 years old with an age range of 22-54 years. Half of the patients had right eye CME and the other half suffered from CME in the left eye. Interferon gamma-1b drops were used in one eye of the participating patients. No patient had active uveitis in the beginning of study. The mean central macular thickness (CMT) obtained by OCT just before administering interferon- gamma-ib drops was 494.50±117.28 micrometer. Moreover, CMT was found to be 474.67±17947 one week after the third drop. The mean CMT decreased in the course of study, but the changes were not statistically significant. The mean visual acuity (VA) before using the first dose of interferon gamma-1b drop was found to be 0.24±0.12 one week after the first drop 0.24±0.15, one week after the secord drop 0.29±0.19, one week after the third drop 0.34±0.22, and finally three month after the third drop 0.30±0.21.

The discrepancy in visual acuity was not found to be statistically significant between base VA (just before interferon gamma – IB instillation) and the one taken one week after the third drop (P= 0.05). The same finding held true when we compared base VA with the one recorded three months after the last dose of the drop (P=0.13). The only statistically significant difference in visual acuity was found between the first evaluation after administering the drop (1 week after the first drop) and a week following the last dose (P=0.01). It is also noteworthy that no statistically significant difference was observed in the IOP during the study. Mean IOP before the drop was 15.30±3.7 *mmhg* and IOP in the last follow-up (3 months after the last drop) was 13.40±2.50. No active uveitis was observed during the study.

Interferons were discovered in 1957 as natural antiviral substances influencing innate and adaptive immune responses.15 These agents have been used for the treatment of autoimmune diseases such as multiple sclerosis.17 They have also been successfully used in treating cystoid macular edema secondary to non-infectious uveitis.13, 14 Interferon type I has two subgroups, namely interferon α and interferon β while interferon type II has only one subgroup, i.e. interferon γ. Other cytokines can influence the action of interferon α or β either as synergistic or antagonistic agents. Interferon type I is mainly produced by dendritic cells. It seems that interferon type I induces production of interferon γ, T-helper cells, CD8+ cytotoxic cells, and natural killer cells during viral infections. It also has an anti-proliferative effect on T-cells. Interferons have immunomodulatory effects rather than immune-suppressive effects[(15)].

Experimental autoimmune uveitis (EAU) in animals can be treated by INF α or β.17 Human studies showed an up-regulation of T regulatory cells in patients with Behçet's disease treated with interferons.18 Furthermore, Wang et al. demonstrated that INF-α-2b up-regulates STAT 5 and down-regulates STAT 3 in conjunction with up-regulation of T regulatory cells and inhibition of IL-17 expressing lymphocytes in melanoma tissue.19 Subcutaneous injection of type I interferons have been used in treating uveitis in Behçet's disease.20 Intravitreal injection of interferons has been used in two patients with advanced age related macular degeneration (AMD), but with minor responses.20 Miller and Sheldon have probed into the effect of interferon-γ on JAK/STAT pathway, a signal transduction pathway represented in human RPE.16 It seems that fluid absorption increases from the retinal to choroidal side of the tissue after stimulation of JAK/STAT pathway

with interferon- γ. There were no apparent changes in cell viability.[16]

In this study with ten patients, we examined the efficacy and safety of interferon- δ in treating Cystoid macular edema secondary to uveitis. We used INF-γ ampoule as an eye drop in patients with CME secondary to uveitis. No evidence of ocular complication or infection was found during the study. Visual acuity of the patients was improved temporarily though this improvement was not statistically significant. CMT changes and intra ocular pressure were not statistically significant either. Intra ocular inflammation based on anterior chamber cell count or vitreous cell count did not deteriorate during the study. This study calls for further studies in this area with a larger number of participants and multiple dosages of INF-γ drops to obtain more accountable results.

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