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The Therapeutic Efficacy of Interferon Alpha-2b in Patients with Primary and Recurrent Pterygium

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ABSTRACT

Background: Pterygium is a growing fibrovascular tissue from the bulbar conjunctiva and can affect the cornea. Pterygium prevalence varies from 10.2% globally in a meta-analysis study, and in Iran, 13.34% was reported. Apart from those that should be surgically removed, there is currently no definitive treatment to eliminate and prevent pterygium growth, and only symptomatic treatment is used (lubrication). On the other hand, research has shown the antiangiogenic and antifibrotic properties of IFN alpha-2b (interferon alfa-2b). The goal of this research was to see how effective IFN alpha-2b is, in treating primary and recurrent pterygium in order to improve quality of life and reduce burden.

Materials and Methods: This study was performed on 34 eyes of 34 consecutive patients suffering from primary and recurrent pterygium who did not indicate surgical treatment during the study. The grade and size of pterygium, visual acuity, refraction, and keratometry were assessed before the intervention, 1, 3, and 6 months after treatment with IFN alpha-2b.

Results: Following treatment with IFN alpha-2b, the mean size of pterygium did not significantly decrease in both groups. Mean UnCorrected Visual Acuity (UCVA) was significantly reduced in both groups. After a 6-month follow-up, the recurrent group's Best-Corrected Visual Acuity (BCVA) improved dramatically. After utilizing IFN alpha-2b, neither group's mean refraction nor mean keratometry improved much.

Conclusion: IFN alpha-2b may not be a proper alternative for surgical approach in patients suffering from primary and recurrent pterygium, but it can be considered an adjunct therapy to prevent a recurrence and burden of disease.

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KEYWORDS
IFN alpha-2b; Pterygium; Quality of life; Primary Pterygium; Recurrent Pterygium

Introduction

Pterygium is a growing fibrovascular tissue which is frequent and in a triangular shape. Pterygium originates from the bulbar conjunctiva and is usually located on the nasal side; that can grow on the cornea [1, 2]. Pterygium prevalence varies from 10.2% to 50% globally [3], and in Iran, 13.34% has been reported [4]. Many risk factors (UV radiation, occupational problems (outdoor work)) are involved in pterygium formation, which makes it challenging to prevent the disease [5]. Pterygium's Population Attributable Fraction (PAF) due to UV radiation is estimated to be 42 percent to 74 percent by the World Health Organization [6].

Patients are urged to avoid going outside in the sun and to use sunglasses [7]. Congestion, redness, visual abnormalities, ocular discomfort, dry eye, vision field limits, and aesthetic issues may all be caused by pterygium, lowering one's quality of life [8]. In pathogenesis, the activation of inflammatory cascades has a significant role in disease recurrence [9]. Recent histological research showed that exposure to ultraviolet radiation can promote pterygium development by a gradual release of various cytokines like interleukins 2, 6, 8 and Vascular Endothelial Growth Factors (VEGF) [10, 11]. Cytokines release causes migration of vascular endothelial cells and fibroblast cells and induces inflammatory reactions, angiogenesis, and fibrovascular tissue formation [12].

Along with inflammatory pathways, some infectious sources (human papilloma virus and herpes simplex virus) and neoplasia conditions (ocular surface squa-

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mous neoplasia) were identified as another contributing factor to pterygium formation and its recurrence [13-15]. Surgery is now the most common therapy for pterygium in most people. However, illness recurrence remains a big concern for those who have been impacted, ranging from 50-80% for a basic old operation (bare sclera) to 3-15 percent for sophisticated procedures (conjunctival autograft). As a result, medicinal measures must be considered in order to avoid illness development and recurrence [16, 17].

Several studies have addressed increasing pterygium recurrence at younger ages, amniotic membrane graft instead of conjunctival autograft, pterygium morphology, and fleshiness of the pterygium [18, 19]. IFN alpha-2b has revealed antiangiogenic, antiviral, and antitumor properties. Therefore, it is used as a therapeutic option for treating eye-related infections (keratoconjunctivitis), inflammatory diseases (Behcet's uveitis), and pre-malignant conditions (conjunctival melanoma, conjunctival squamous cell neoplasia, and others) [20-24]. Because IFN alpha-2b affects pathologic factors that make up the pterygium, we aimed to examine the IFN alpha-2b effectiveness in treating primary and recurrent pterygium.

Materials and Methods

This case series study was performed on 34 eyes of 34 consecutive patients who were suffering recurrent and primary pterygium referred to the ophthalmology clinic of the Baghiatallah Hospital in Tehran between 2018 and 2019. According to one ophthalmologist's diagnosis, all patients had unilateral pterygium and did not suggest surgical therapy throughout the trial (SHD). They all had at least one prior surgical therapy in the recurrent group. Patients were excluded with: any topical ophthalmic drug use over the last six months, history of allergy to interferons or its related, ophthalmological disorders (except for refractive errors), and pregnancy or breastfeeding. The study questionnaire consisted of two parts; the first included general characteristics (demographics and socioeconomic status), and the second included clinical examinations.

A single ophthalmologist did all investigations. We graded the primary pterygium based on the previously described Tan system [18]. Grade 1, in which episcleral vessels are still visible under pterygium; Grade 2, in which episcleral vessels are relatively visible under pterygium; Grade 3, in which episcleral vessels are obscure by pterygium. According to Welch's research, the pterygium size was measured on the corneal surface, encompassing vertical and horizontal pterygium length. The largest diameter was taken [25]. All measurements were performed by a Haag-Streit Slit lamp (BQ 900, Haag-Streit, Koeniz, Switzerland) with a standard zoom of sixteen.

All patients had two intralesional injections of IFN alpha-2b (Pooyeshdarou Biopharmaceutical Company, CO.) 1 ml, with a concentration of 3.000.000 units/mL, subconjunctivally done. The first injection was done on the first visit, and the second injection was performed at the end of the first month. Simultaneously, the patients used a topical drop of IFN alpha-2b (Pooyeshdarou Biopharmaceutical Company, CO.) with a concentration of 1.000.000 units/mL. Table 1 shows the drugs intake method; all dosages were similar to a previous study. All patients had an ophthalmic examination, which included UCVA and BCVA, refraction, keratometry, pterygium size, clinical state of the cornea and lens, intraocular pressure, and retina.

The first day (before the first intralesional injection), the end of the first month (before the second intralesional injection), the third month, and the sixth month were all examined. All patients gave written informed consent before the study, and the Baqiyatallah ethical committee ethically approved the study protocol 111 (IR.BMSU.BAQ.REC.1396.471). For statistical analysis, results were presented by mean ± Standard Deviation (SD) for quantitative variables. The change in study parameters within the six months of assessment was analyzed by the Repeated Measure ANOVA and Friedman. P values ≤ 0.05 are considered statistically significant. The statistical software SPSS version 16 for Windows (IBM, Armonk, New York) was used for the statistical analysis.

Results

18 eyes of 18 patients (12 male, 6 female, and mean age: 42.11) with primary pterygium and 16 eyes of 16 patients (10 male, 6 female, and mean age: 51.87) with recurrent pterygium were included in the study. Right and left eyes involvement were recorded in the primary group 11 (68.1%) and 7 (38.9%), and the recurrent group was 9 (56.3%) and 7 (43.7%), respectively. Three patients in the main group and three patients in the secondary group did not attend the six-month follow-up.

Grading and mean size of pterygium did not alter in either group; in the recurrent group, all patients were grade four (extensive fibrovascular tissue on the cornea) and did not change during the course of the trial. Table 2 shows the primary group grading. Mean Un-Corrected Visual Acuity (UCVA) in both groups and Best-Corrected Visual Acuity (BCVA) in the recurrent group were significantly corrected after a six-month follow-up. Tables 2 and 3 show the study parameters in the primary and recurrent pterygium groups.

Table 1. Schedule for topical drop IFN alpha-2b consumption.

Duration	IFN alpha-2b
First month	Every 6 hours
Second month	Every 8 hours
Third month	Every 12 hours

Table 2. The study variable changes in patients with primary pterygium.

Parameter		Before	1-month	3-month	6-month	P-value
Pterygium Grading	Grade one (n)	1	1	1	1	0.92
	Grade two (n)	12	12	12	10	0.88
	Grade three (n)	5	5	5	4	0.91
Longitudinal size of pterygium (mm)		2.48 ± 1.41	2.87 ± 1.28	2.81 ± 1.34	2.68 ± 1.37	0.81
Vertical size of pterygium (mm)		1.3 ± 1.27	1.26 ± 1.27	1.29 ± 1.25	1.23 ± 1.27	0.73
Uncorrected visual acuity (LogMAR)		0.17 ± 0.20	0.17 ± 0.20	0.17 ± 0.17	0.13 ± 0.25*	0.03*
Best Corrected visual acuity (LogMAR)		0.06 ± 0.08	0.05 ± 0.06	0.04 ± 0.06	0.04 ± 0.06	0.09
Refraction (diopters)		0.97 ± 1.09	0.87 ± 0.94	1.05 ± 1.05	1.23 ± 1.48	0.12
Keratometry (diopters)		2.04 ± 2.10	1.99 ± 2.12	1.95 ± 2.06	1.98 ± 2.22	0.63

Note: *P-value<0.05, repeated measures ANOVA and Friedman, as appropriate.

Table 3. The study variable changes in patients with recurrent pterygium.

Parameter	Before	1-month	3-month	6-month	P-value
Longitudinal size of pterygium(mm)	2.58 ± 1.11	2.37 ± 1.16	2.43 ± 1.00	2.43 ± 1.27	0.77
Vertical size of pterygium (mm)	2.02 ± 1.35	1.95 ± 1.35	1.88 ± 1.45	1.55 ± 1.37	0.65
Uncorrected visual acuity (LogMAR)	0.28 ± 0.18	0.31 ± 0.20	0.25 ± 0.20	0.28 ± 0.17	0.02*
Best Corrected visual acuity (LogMAR)	0.17 ± 0.16	0.15 ± 0.17	0.13 ± 0.14	0.16 ± 0.15	0.03*
Refraction (diopters)	1.62 ± 1.20	1.50 ± 1.17	1.70 ± 1.28	1.84 ± 1.01	0.22
Keratometry (diopters)	43.60 ± 0.63	43.60 ± 0.53	43.70 ± 0.59	43.60 ± 0.50	0.85

Note: *P-value<0.05, repeated measures ANOVA and Friedman, as appropriate.

Discussion

Quality of life decreases and visual impairment are pterygium's most crucial side effect [8]. Pterygium prevalence varies from 10.2% to 50% globally [5], and in Iran, 13.34% has been reported (in rural areas more than other studies) [4]. UV and sunlight are the most major risk factors, which vary accordingly on where you live, your age, gender, ethnicity, outdoor employment, and other factors [5]. The prevalence of pterygium in Iran in some areas is even higher than tropical regions, which are called the pterygium belt. Therefore, it is essential to find a treatment other than pterygium surgery.

Pterygium is a fibrovascular tissue which needs surgery if it causes chronic irritation, long-term eye discomfort, visual axis threatening (size>3-4 mm corneal invasion) [26], progressive growth, eye movement restriction, and marked corneal astigmatism. Atypic pterygium can be the origin of a malignant proliferation (carcinoma in situ and squamous cell carcinoma), which must always be considered [27]. Apart from those that must be surgically removed, there is presently no definite therapy for pterygium growth that can be utilized to eradicate and prevent it, and only symptomatic treatment is performed (lubrica-

tion). IFN was first introduced in 1952 and is divided into two types. IFN alpha is in type one, and its most crucial activity with direct and indirect effects on antiproliferation. The direct impact inhibits cell proliferation in JAK-STAT pathway, and the indirect effect inhibits angiogenesis [28]. Pterygium formation is composed of two essential parts, epithelial cell proliferation, and neovascularization, which can inhibit by IFN alpha-2b [29, 30].

Our study suggests that IFN alpha-2b cannot be used as a main therapeutic regimen for primary and recurrent pterygium. It should only consider a supplemental regimen in pterygium treatment. Assessing IFN alpha-2b efficacy on disease progression needs further studies with an extended follow-up. The effectiveness of IFN alpha-2b has been shown in two case studies. For three weeks, a 32-year-old athletic lady with recurrent pterygium was treated with an IFN alpha-2b drop containing 1 million units/mL four times a day. In another study, a 52-year-old athletic man with recurrent pterygium was treated by instilling IFN alpha-2b drop 1 million units/mL four times a day for four weeks in 2015 [21, 31]. Although these two case reports suggest the influential role of IFN alpha-2b on the treatment of pterygium [19, 21], our study could not support such evidence. We emphasize that IFN alpha-2b cannot be the only treatment, and more studies are needed. IFN alpha-2b, in a study by Yin, et al. in 2019 was an effective and safe adjunct therapy after the bare sclera technique to reduce pterygium recurrence [32].

In comparison to the first visit, the six-month visit demonstrated statistical improvement in uncorrected visual acuity in both groups and best-corrected visual acuity in the recurrent pterygium group. Other ophthalmological measures did not show any significant changes. However, UCVA and BCVA were not more than a single line; this improvement clinically was observed too. Vision Improvement may be due to the interferon performance in improving high-order aberrations and dry eye, which are among the shortcomings of our study and are recommended for measurements in future studies. On the other hand, visual acuity is a subjective variable; it does not make sense that this visual improvement is attributed only to treatment. Several factors, such as ocular surface condition, patient cooperation, and environmental factors like brightness quality, can affect visual acuity.

Moreover, it is unlikely that IFN alfa-2b improves visual acuity without change in pterygium grading, pterygium size, refraction, and keratometry. However, we recommend that these variables will be considered in the subsequent studies. The observational character of our investigation, the small number of patients, and the lack of high-order aberration and dry eye measurements are all drawbacks that should be addressed in future studies.

Conclusion

Although IFN alpha-2b has many different features and may be effective as adjuvant therapy, IFN alpha-2b may not be a proper alternative for surgical approach in patients suffering from primary and recurrent pterygium, but it can be considered as an adjunct therapy to prevent a recurrence. Further studies are needed to demonstrate its efficacy in disease progression and as a Complementary therapy.

Conflict of Interest

None

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