Research Square

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The Efficacy of 0.1% Tacrolimus Eye Drop for Noninfectious, Non-Necrotizing Anterior Scleritis

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Research article

Keywords: scleritis, tacrolimus eye drop, steroid, hyperemia, pain, intraocular pressure

Posted Date: June 25th, 2019

DOI: https://doi.org/10.21203/rs.2.10618/v1

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Abstract

BACKGROUND: To examine the efficacy of 0.1% tacrolimus eye drops in the treatment of noninfectious, non-necrotizing anterior scleritis. METHODS: This prospective, single-arm study included nine patients (4 males and 5 females; mean age = 59.4 years, standard deviation = 10.5) with anterior scleritis. All patients were first treated with steroids for 1 month and then switched to tacrolimus eye drops alone. We defined baseline as the initiation of steroid or tacrolimus eye drops. Hyperemia and pain were scored before each treatment, at 1 and 2 weeks, and at 1 month after initiation of each treatment by using 5 grades (0 = none; 1+ = mild; 2+ = moderate; 3+ = severe; 4+ = extremely severe). Intraocular pressure (IOP) was also measured from baseline to 6 months after initiating tacrolimus eye drops. Safety was assessed based on the severity and the incidence of adverse events. RESULTS: The scores of hyperemia and pain had significantly decreased from baseline by 1 week after initiating tacrolimus eye drops (both $P < 0.05$). No significant reduction was observed with steroid treatment throughout the 1-month period in terms of both scores. Tacrolimus eye drops elicited statistically significant differences in mean IOP over the course of treatment ($P = 0.02$). No additional medications were required to provide relief in any of the patients receiving tacrolimus treatment. No patient had infectious adverse events after initiation of tacrolimus treatment. CONCLUSIONS: Topical tacrolimus may effectively and immediately reduce clinical signs and symptoms of noninfectious, non-necrotizing anterior scleritis. TRIAL REGISTRATION: This trial was prospectively registered on 16/10/2015 under the number (UMIN000034460).

Background

Scleritis is an ocular inflammatory disease that is characterized by severe scleral redness and substantial pain levels. Scleritis can be associated with a chronic course as well as Mooren ulcers, Stevens-Johnson syndrome, and ocular cicatricial pemphigoid, and can lead to impaired quality of vision and life.[1] It is important to know whether scleritis is caused by infection or systemic disease, because the appropriate treatment differs accordingly; infectious scleritis requires antiviral or antibiotic agents, whereas scleritis associated with systemic disease requires systemic immunosuppressive medications.[2]

The main treatment of any type of noninfectious scleritis typically involves topical and/or systematic steroids. Additionally, there have been several reports that subconjunctival triamcinolone acetonide injection may be useful as adjuvant therapy for severe scleritis.[3, 4] However, we sometimes encounter patients who are refractory to these steroid medications. Although additional steroids may be required to relieve patient symptoms, they can cause adverse effects, such as cataract, infection, steroid-induced elevation of intraocular pressure (IOP), glaucoma, eyelid skin atrophy, and depigmentation with barrier impairments.[5-7]

To overcome these problems, alternative therapeutic medications for scleritis have been sought. There have been several reports on the effects of nonsteroidal topical immunosuppressive medications (e.g., tacrolimus and cyclosporine) for relieving patient symptoms; these agents can reduce the rate of serious side-effects from steroids used to treat any allergic or immunological disorders.[8-14] However, there have

been few reports of the use of topical tacrolimus in cases with scleritis and the therapeutic effects of this treatment remain poorly understood.[1, 13] Moreover, there has been no prospective comparative study of the therapeutic effects of steroids or topical tacrolimus use in the same eye.

Thus, the purpose of this study was to examine the efficacy of 0.1% tacrolimus eye drops for the treatment of noninfectious and non-necrotizing anterior scleritis.

Methods

The present investigation was a single-center, prospective, single-arm study of 9 cases. It was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Review Board of Tsurumi University Dental Hospital (Kanagawa Prefecture, Japan; IRB No.1312). The clinical trial registration ID number is University Hospital Medical Information Network (UMIN) 000034460. All participants provided their written informed consent to participate in the study.

Patients and treatment

Nine eyes from 9 patients with noninfectious anterior scleritis were first treated with steroids for 1 month and then switched to tacrolimus eye drops alone. No patient with necrotizing and posterior scleritis was included. These eyes were treated with tacrolimus (TALYMUS®, Senju Pharmaceutical Co., Ltd., Osaka, Japan) eye drops alone between February 2016 and April 2017.

The exclusion criteria in this study were as follows: patients with a history of allergic hypersensitivity or known hypersensitivity to any compound or diluting agent of tacrolimus; a history of using tacrolimus eye drops; presence of any ocular condition that could affect the study parameters and/or patient safety (e.g., glaucoma requiring medication or laser treatment, clinically significant blepharitis, uveitis, or pterygium); having undergone ocular surgical intervention within 3 months prior to the study and/or a history of refractive surgery within 6 months before the study; presence of active ocular infection (bacterial, viral, or fungal), or a positive history of an ocular herpetic infection at initiation of this study; any systemic diseases that may affect the ocular surface (e.g., rheumatoid arthritis, systemic lupus erythematosus, relapsing polychondritis, and antineutrophil cytoplasmic antibody-associated vasculitis, and ulcerative colitis); patients who were pregnant, nursing, or planning a pregnancy; patients who smoked; or used contact lenses.

All patients were administered 1 drop of tacrolimus eye drops twice or four times a day, with other treatments discontinued from the beginning of this observation. No patient was treated with subconjunctival triamcinolone acetonide injection, oral non-steroidal anti-inflammatory drugs (NSAIDs), immunomodulatory therapy (IMT; i.e., antimetabolite agents, T-cell inhibitor agents, or alkylating agents), and biological response modifiers (BRMs; i.e., anti-TNFα agents, anti-interleukin 2 receptor agents, anticluster of differentiation 20 agents, and anti-interleukin 6 receptor agents) before and during the

observation. We defined baseline as the point of initiation of steroids and of initiation of tacrolimus and defined the period of treatment with steroids as the control period.

Outcomes

Changes in hyperemia and pain scores were observed before starting each treatment, and at 1 and 2 weeks as well as 1 month after initiating each treatment type. Hyperemia as well as pain were assessed using a 5-point grading system (0 = normal; 1+ = mild; 2+ = moderate; 3+ = severe; 4+ = extremely severe); grading of hyperemia was based on a previous report.[15] The efficacy endpoint was assessed based on the extent of change in the scores of hyperemia and pain at the end of treatment. Hyperemia and pain scores were also compared after treatment with steroids and tacrolimus eye drops. IOP was measured from baseline to 6 months after initiating tacrolimus eye drops with non-contact tonometry (NIDEK NT-4000, Gamagori, Japan). Safety was assessed based on the incidence and the severity of adverse events.

Statistical analysis

The data were analyzed using Stata 14 software (StataCorp LP, College Station, TX) and Prism version 8.00 (Graphpad Software, Inc.).

The hyperemia and pain scores were analyzed using a generalized mixed linear regression model. Data were presented as adjusted means ± 95% confidence intervals (CI), ± standard deviation (SD), or ranges. A one-way repeated measures analysis of variance was performed in order to determine if there were differences in IOP. P value less than 0.05 was considered statistically significant.

Results

Characteristics of patients with scleritis

Demographic information of all patients in this study is shown in Table 1. Of the 9 patients with scleritis, 5 (44%) were men and 4 (56%) were women, with a mean age of 59 years (standard deviation, 11 years; range 44–73 years), and a follow-up period of 1 month with steroid treatment before commencing tacrolimus eye drops. All patients had unilateral scleritis. At the beginning of the observation, 8 patients (88.9%) had diffuse and 1 patient (11.1%) had nodular anterior scleritis. No necrotizing or posterior scleritis cases were included. No ocular complication was observed in any of the patients during the follow-up period. All patients complained of a mild, well-tolerated burning sensation upon application of the eye drops. No patient self-discontinued treatment during the study course, except for 1 female patient, and no patient had any infectious adverse event (e.g., elevated IOP, hordeolum, chalazion, lid herpes, herpetic keratitis, bacterial keratitis, or corneal erosion) after initiation of tacrolimus eye drop use.

Immediate change in hyperemia scores after initiation of tacrolimus eye drop treatment

A comparison of changes in hyperemia scores before and after intervention with tacrolimus eye drops is shown in Figure 1. Hyperemia scores during tacrolimus eye drop treatment significantly improved, as compared with the control period. The adjusted mean hyperemia score at baseline was 3.98 (95% CI, 3.65–4.31) for patients who were treated with steroids, and 3.68 (95% CI, 3.35–4.01) for patients subsequently treated with tacrolimus eye drops alone ($P > 0.05$). The hyperemia score was significantly reduced to 2.85 (95% CI, 2.55–3.15) at 1 week, 1.90 (95% CI, 1.58–2.23) at 2 weeks, and 1.00 (95% CI, 0.61–1.39) at 1 month after initiation of tacrolimus eye drops alone (all $P < 0.001$). No significant reduction was observed in the control throughout 1 month; 4.00 (95% CI, 3.73–4.37) at 1 week, 3.98 (95% CI, 3.65–4.31) at 2 weeks, and 3.97 (95% CI, 3.55–4.40) at 1 month.

Immediate changes in pain scores after initiation of tacrolimus eye drop treatment

A comparison of changes in pain scores before and after intervention with tacrolimus eye drops is shown in Figure 2. Pain scores during tacrolimus eye drop treatment improved significantly as compared with the control period. The adjusted mean pain score at baseline was 3.82 (95% CI, 3.31–4.35) during the steroid treatment, and 3.40 (95% CI, 2.87–3.92) during the subsequent treatment with tacrolimus eye drops alone ($P > 0.05$).

The pain score was significantly reduced to 2.49 (95% CI, 2.02–2.96) at 1 week, 1.51 (95% CI, 1.04–1.98) at 2 weeks, and 0.83 (95% CI, 0.31–1.35) at 1 month after initiation of tacrolimus eye drop treatment alone. No significant reduction was observed throughout the 1-month control period; 3.58 (95% CI, 3.10–4.06) at 1 week, 3.27 (95% CI, 2.80–3.74) at 2 weeks, and 3.26 (95% CI, 2.69–3.83) at 1 month (all $P < 0.001$).

Changes of IOP after initiation of tacrolimus eye drop treatment

Changes of IOP are shown in Figure 3. IOP gradually decreased from baseline to 1 week after beginning tacrolimus eye drop treatment. Tacrolimus eye drops elicited statistically significant differences in mean IOP over the time course of treatment ($F(6, 47) = 5.76$, $P = 0.02$). Mean IOP before beginning tacrolimus eye drop in patients with scleritis was 20.6 ± 5.8 mmHg and decreased to 18.7 ± 4.4, 17.6 ± 3.5, 15.6 ± 1.8, 15.8 ± 1.9, 16.2 ± 2.1, and 16.1 ± 1.6 at 1 and 2 weeks, and 1, 2, 3, and 6 months after initiation of treatment.

Case of self-discontinuation of tacrolimus eye drop treatment and reactivation of scleritis

Representative photographs of changes in the sclera of the right eye of a patient after the use of tacrolimus eye drops are shown in Figure 4. A 69-year-old female patient with a diagnosis of diffuse anterior scleritis with hyperemia with dilation of many vessels and thinner diffuse chemosis came to our outpatient clinic with a complaint of unbearable right eye pain lasting 1 week. Although she was administered 0.1% betamethasone 4 times a day for 1 month, her pain worsened and IOP elevated gradually. Thus, we stopped the steroid eye drop treatment, and then started 0.1% tacrolimus eye drop treatment in order to control diffuse anterior scleritis (Figure 4A). After 1 week, inflammation started to decrease (Figure 4B). Hyperemia had almost resolved after 1 month (Figure 4C), but the patient interrupted her treatment. Reactivation of scleritis was observed at 2 months after initiation of tacrolimus eye drop treatment (Figure 4D); thus, we restarted tacrolimus treatment and the hyperemia and pain gradually improved at 3 months and 6 months (Figure 4E and 4F).

Discussion

Here, we compared the effects of steroid treatment for 1 month with those of subsequent treatment with tacrolimus eye drops only, in the same eye of patients with noninfectious and non-necrotizing anterior scleritis cases refractory to standard conventional steroid treatments. We found that 0.1% tacrolimus eye drops had immediate beneficial effects on the clinical outcomes of these eyes.

Scleritis is broadly divided into two types according to the site of development (i.e., anterior and posterior); moreover, anterior scleritis can be subdivided into 3 types (i.e., diffuse, nodular, and necrotizing).[16, 17] Necrotizing and posterior scleritis have a much higher risk of complications (e.g., keratitis, scleral thinning, cataract, uveitis, glaucoma, macular edema, and retinal detachment) and worse visual outcome than other types of scleritis.[18] However, in our study, all patients had unilateral diffuse or nodular scleritis, and 0.1% tacrolimus eye drops showed efficacy in eyes that were refractory to steroid treatments. In the treatment of scleritis, we have often encountered cases that were extremely resistant to conventional steroid treatments. When considering the use of additional anti-inflammatory drugs for treating chronic ocular surface disorders that are refractory to corticosteroids, such as scleritis, it is important to consider the drug's efficacy and safety for controlling inflammation, and its corticosteroid-sparing potential. We have often experienced that tacrolimus was effective after steroid pretreatment in a clinical setting, and thus we did not conduct a randomized controlled trial or a crossover trial, but rather performed a single-arm study, due to ethical considerations. There have been some reports on treating scleritis with tacrolimus ointment,[1, 13, 19] but these were retrospective studies or case reports, and were not comparative studies of tacrolimus and steroids, and used steroids in combination with tacrolimus. No previous study had reported results of a prospective single-arm study of the immediate effects of topical tacrolimus in anterior scleritis.

Since 2005, 0.1% cyclosporine aqueous ophthalmic solution became available and there were some reports on its therapeutic effects on conventional treatment-resistant ocular surface diseases, including scleritis.[8, 20-22] Similarly, some studies have reported the efficacy and safety of tacrolimus ointment[1, 11-13, 19, 23, 24] and tacrolimus ophthalmic suspension[10, 14, 25]in the treatment of ocular inflammatory diseases. Cyclosporine binds to cyclophilin, while tacrolimus binds to FK506 protein; these agents exert pharmacological activities, such as inhibition of cytokine (e.g., interleukin [IL]-2, IL-4, IL-5 and interferon [IFN]-γ) production and suppression of mast cell degranulation by inhibition of calcineurin activation. Scleritis is an autoimmune disease; when complement binds to the immune complex deposited in the scleral blood vessels, inflammatory cells, such as lymphocytes, mast cells, and macrophages are recruited, and vasculitis occurs. Thus, tacrolimus and cyclosporine are thought to improve scleritis by suppressing these reactions. However, tacrolimus has also been reported to inhibit calcineurin approximately 100 times more effectively than cyclosporine.[26] Thus, tacrolimus may be more effective than cyclosporine in the treatment of ocular surface inflammatory diseases, including scleritis. However, considering the molecular mechanisms, steroids have more diverse effects than calcineurin inhibitors. Tacrolimus may have had a synergistic effect with those caused by the preceding steroid treatment, which may have been the reason for the early efficacy (1 week after starting tacrolimus). Therefore, it is necessary to compare between a tacrolimus/steroid treatment group and a tacrolimus-only group in future.

According to the American Academy of Ophthalmology, because scleritis is associated with a systemic disease in approximately 40% of patients,[16] oral NSAIDs may be the first choice in patients with noninfectious unilateral diffuse or nodular anterior scleritis.[27-29] On the other hand, steroids, IMT, and BRMs have been reported to be useful in patients with bilateral necrotizing scleritis or scleritis associated with systemic disease.[10, 27, 30-34] However, in Japan, because the definitive treatment of scleritis is vague in actual clinical practice, topical and/or oral steroids are typically used as first-line treatment instead of oral NSAIDs, even if the scleritis is mild. In fact, Keino et al. reported that NSAIDs were used in only 5 of 83 (6.0%) patients with scleritis,[17] while none of the patients in the present study were treated with NSAIDs. We must consider the systemic side effects of these internal medications. The most notable adverse event in topical treatment is infections, such as herpes, whereas the side effects reported with systemic tacrolimus are renal toxicity, hyperglycemia, and hypertension,[13] but these risks may be considered low in topical treatment. Thus, topical tacrolimus is expected to be an effective and safe treatment for refractory scleritis.

In terms of changes in hyperemia, the scores significantly decreased from baseline to 1 week after beginning tacrolimus eye drops. This was a more immediate improvement than that achieved in previous reports on refractory inflammatory ocular surface diseases.[1, 10, 13, 35, 36] In terms of changes in pain, the scores were significantly decreased 1 week after beginning tacrolimus eye drops, similar to the hyperemia. Although all patients complained of a mild burning sensation upon application, it was well-tolerated and no patient discontinued treatment because of the burning sensation. Moreover, because the chief complaint of patients with scleritis may be pain, it is valuable to achieve pain relief in 1 week.

However, as Figure 4 shows, if tacrolimus treatment is interrupted suddenly, despite a good course, symptoms and findings may be reactivated and tacrolimus may be less effective after restarting treatment. Thus, when the condition gets better, the number of eye drops is gradually decreased, and then proactive therapy may also be effective for treatment of scleritis as suggested in medical treatment for other allergic and immunological diseases[37].

In the IOP, it was unclear whether IOP was decreasing by stopping steroids or starting with tacrolimus. Thus, we assessed the changes in IOP from initiation of tacrolimus eye drops, without comparing the changes among them. IOP gradually decreased from baseline to 1 week and a significant difference was observed throughout the 6-month period. It is widely known that steroids may elevate IOP, but IOP is not likely to elevate during treatment with tacrolimus, as previously reported.[13] Nevertheless, we have found that some eyes with tacrolimus eye drops had elevated IOP,[14] but the use of non-contact tonometry may have been influenced by the poor condition of the eyelid (e.g., lid swelling and hard skin), or by the secondary difficulty in lid opening or closure. In this study, we were able to evaluate the IOP more accurately because eye-opening in all patients was good. Therefore, it was thought that there was no influence of the eyelid, and IOP after initiation of tacrolimus treatment may not be elevated.

CONCLUSIONS

Although the small sample size and the lack of washout period between steroids and tacrolimus eye drops were the main limitations of the current study, the results of this study suggested that 0.1% tacrolimus eye drops had immediate beneficial effects on clinical outcomes in patients with noninfectious and non-necrotizing anterior scleritis refractory to standard conventional steroid treatments.

Abbreviations

IOP; intraocular pressure

NSAIDs; non-steroidal anti-inflammatory drugs

IMT; immunomodulatory therapy

BRMs; biological response modifiers

CI; confidence intervals

SD; standard deviation

IL; interleukin

IFN; interferon

Declarations

Ethics approval and consent to participate

It was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Review Board of Tsurumi University Dental Hospital (Kanagawa Prefecture, Japan; IRB No.1312). The clinical trial registration ID number is University Hospital Medical Information Network (UMIN) 000034460. All participants provided their written informed consent to participate in the study.

Consent for publication

All participants in this study signed written consent forms for the publication of their relevant clinical data.

Availability of data and material

Data and materials are available upon request from the corresponding author at g.h.yazu@gmail.com.

Competing interests

The authors declare that there is no competing interest.

Funding

No sponsor or funding organization played role in designing or conducting this research. Also the authors have no conflicts of interest to declare.

Authors' contributions

DM and HF participated in the design of the study. HY drafted the manuscript. HY and DM carried out the statistical analysis. HY prepare of the manuscript. All authors read and approved the final version manuscript.

Acknowledgements

The authors thank Editage Company for English language editing.

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Table

Table 1. Demographics of patients

Eyes	9
Sex, n (%)	
Male	4 (44.4)
Female	5 (55.6)
Age (y) ± SD	59.4 ± 10.5
Laterality, n (%)	
Unilateral	9 (100)
Bilateral	0 (0)
Scleritis type, n (%)	
Anterior Diffuse	8 (88.9)
Nodular	1 (11.1)
Necrotizing	0 (0)
Posterior	0 (0)
Ocular complications, n (%)	
Peripheral ulcerative keratitis	0 (0)
Herpetic keratitis	0 (0)
Anterior herpetic uveitis	0 (0)
History of disorders, n (%)	
Hypertension	2 (22.2)
Diabetes mellitus	2 (22.2)
Heart disease	2 (22.2)
Herpetic keratitis	1 (11.1)
Anterior herpetic uveitis	1 (11.1)
Other allergic complications, n (%)	
Asthma	1 (11.1)
Atopic dermatitis	0 (0)
Treatments before tacrolimus eye drop, n (%)	
Oral non-steroidal anti-inflammatory drugs (NSAIDs)	0 (0)
0.1% fluorometholone (FLM)	0 (0)
0.1% betamethasone (BEM)	9 (100)
Oral steroid	1 (11.1)
Topical cyclosporine	0 (0)
Topical tacrolimus	0 (0)
Immunomodulatory therapy (IMT)	0 (0)
Biologic response modifier (BRM)	0 (0)

Figures

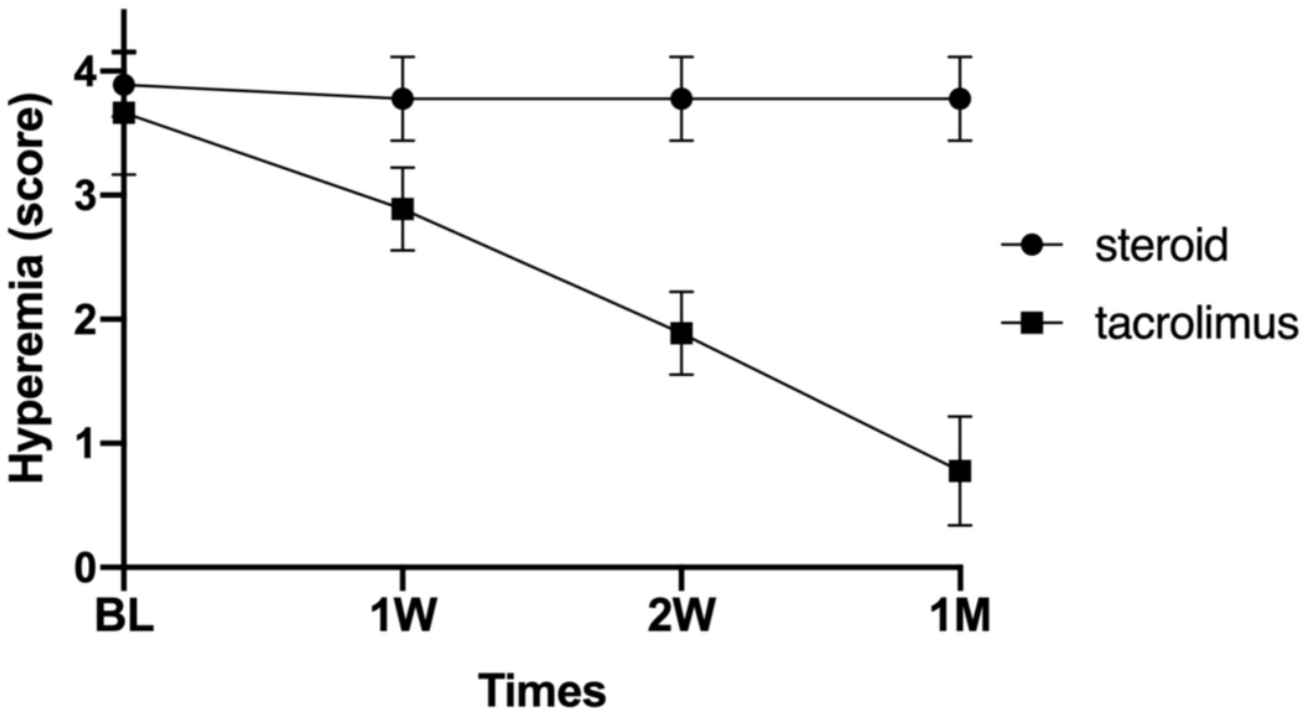


Figure 1

A comparison of changes in hyperemia scores before and after intervention with tacrolimus eye drops Hyperemia scores significantly dropped from baseline 1 week after beginning tacrolimus. The adjusted mean hyperemia score at baseline was 3.98 (95% CI, 3.65–4.31) for patients who were treated with steroids, and 3.68 (95% CI, 3.35–4.01) for patients subsequently treated with tacrolimus eye drops alone ($P > 0.05$). After 1 month, the hyperemia score was significantly reduced to 1.00 (95% CI, 0.61–1.39) with tacrolimus eye drops alone, whereas no significant reduction was observed with steroid treatment alone (95% CI, 3.55–4.40).

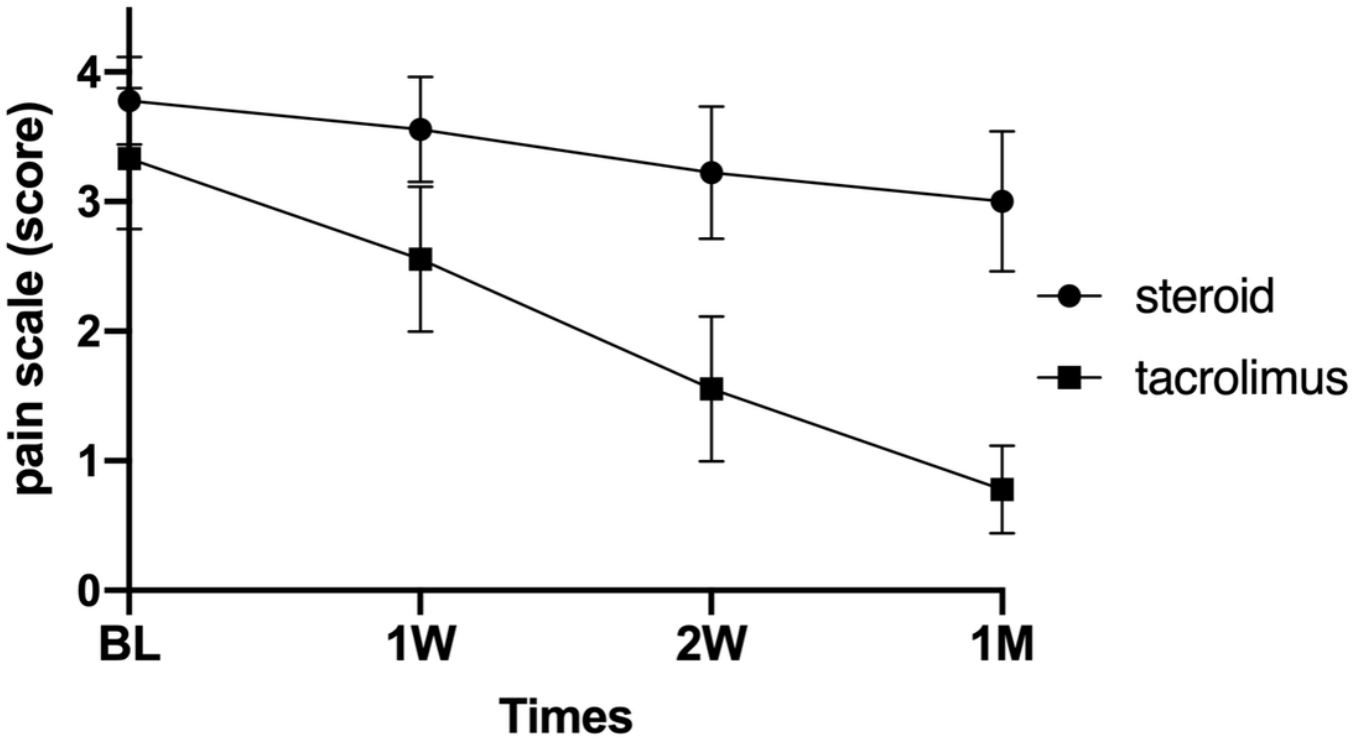


Figure 2

A comparison of changes in pain scores before and after intervention with tacrolimus eye drops Pain scores significantly dropped from baseline 1 week after beginning tacrolimus. The adjusted mean pain score at baseline was 3.82 (95% CI, 3.31–4.35) for patients who were treated with steroids, and 3.40 (95% CI, 2.87–3.92) for the patients subsequently treated with tacrolimus eye drops alone ($P > 0.05$). After 1 month, the pain score was significantly reduced to 0.83 (95% CI, 0.31–1.35) with tacrolimus eye drops alone, whereas no significant reduction was observed with steroid treatment alone (95% CI, 2.69–3.83).

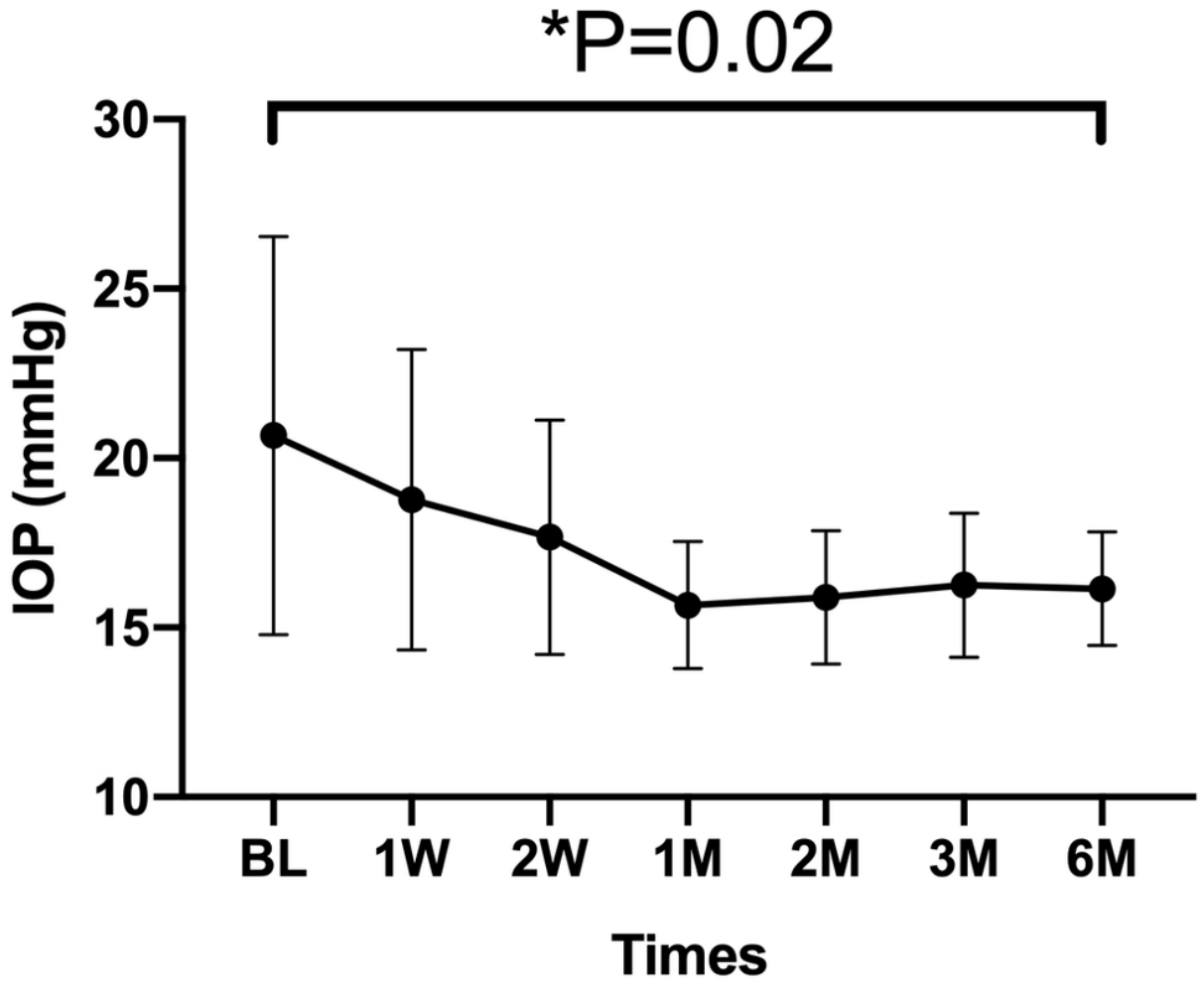


Figure 3

Changes in intraocular pressure (IOP) after initiation of tacrolimus eye drop treatment IOP gradually decreased from baseline to 1 week after beginning tacrolimus eye drops. Tacrolimus eye drops elicited a statistically significant difference in the mean IOP over the time course of treatment (P = 0.02). The mean IOP before beginning tacrolimus eye drops was 20.6 ± 5.8 mmHg and decreased to 16.1 ± 1.6 at 6 months after initiation.

Figure 4

Changes in the scleritis after initiation of tacrolimus eye drop treatment Treatment with 0.1% tacrolimus eye drops was started to control diffuse anterior scleritis in the right eye of a 69-year-old woman (Figure 4A). After 1 week, inflammation started to decrease (Figure 4B). Hyperemia was almost resolved after 1

month (Figure 4C), but the patient interrupted her treatment. Because reactivation of scleritis was observed at 2 months after initiation of tacrolimus eye drop treatment (Figure 4D), we restarted tacrolimus treatment and her hyperemia and pain scale gradually improved at 3 months and 6 months (Figure 4E and 4F).