

# Topical tacrolimus in ocular Graft Versus Host Disease

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## Research Article

**Keywords:** topical tacrolimus, ocular surface, Graft Versus Host Disease

**Posted Date:** April 13th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-327505/v1>

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# Abstract

**Purpose:** To evaluate the safety and efficacy of topical tacrolimus eye drops in the treatment of patients with ocular Graft Versus Host Disease (GVHD).

## Methods

Ten consecutive patients with ocular GVHD were included retrospectively. All patients were treated with topical tacrolimus (0.01% - 0.03%) twice daily. Five patients were given adjunctive topical steroids for 4 to 6 weeks. The outcome measures included improvement of symptoms of photophobia, ocular pain and discharge and signs of superficial punctate keratitis and conjunctival hyperemia. Clinical assessment was carried out before, during and on the last visit after treatment.

## Results

There were 9 males and 1 female patients. The mean age was 30 years (range 5 to 51). All patients had bilateral ocular involvement. Duration of treatment ranged from 2 to 22 months (mean 6.5 months). There was improvement of symptoms in 8/10 (80%), superficial punctate keratitis in 8(40%) out of the 20 eyes and conjunctival hyperemia in 12 (66%) out of 18 eyes. The response to treatment was noted to be late following initiation of therapy (Average 3 weeks; range 1 to 8 weeks). Patients given adjunctive steroids responded faster. The main adverse ocular side effects were burning sensation, redness and swollen lids.

## Conclusion

Topical tacrolimus is a safe and effective long-term therapy in the treatment of patients with ocular GVHD. Adjunctive short-term use of topical steroids may lead to faster response to topical tacrolimus therapy. Patients should be encouraged to continue use of topical tacrolimus as the onset of action may be delayed.

## Background

Graft-Versus-Host Disease (GVHD) is a major complication following allogeneic hematopoietic stem cell transplantation (HSCT). It is an inflammatory response derived from donor cell infiltration and directed against host tissues including skin, gastrointestinal tract, liver, lung, oral mucosa and the eyes.<sup>1</sup> GVHD occurs in two forms: acute or chronic with different clinical presentations. Ocular involvement may occur in both forms of the disease; however, it is more common and more severe in the chronic form of the disease.<sup>2</sup> Ocular GVHD is a spectrum of clinical manifestations, affecting all layers of the eye including the lid, lacrimal gland, conjunctiva, cornea and less frequently the vitreous, retina and choroids.<sup>2</sup> Dry eye syndrome is the most common ocular complication in patients with GVHD.<sup>3</sup>

The pathogenesis of GVHD is not clearly understood. GVHD is an immune-mediated disease that results from complex interactions between donor and recipient adaptive and innate immune systems.<sup>1</sup> Donor-derived T lymphocytes are thought to be the primary effector cells in the pathogenesis of GVHD leading to inflammation of the involved tissues. Inflammation of the lacrimal gland, conjunctiva and cornea seems to play the major role in the pathogenesis of ocular disease in patients with GVHD.<sup>1</sup> Therefore, reducing ocular surface inflammation plays an essential role in the management of patients with ocular GVHD. Topical steroids have been used in the treatment of ocular surface inflammation in patients with GVHD. However, prolonged use of topical steroids is associated with high incidence of ocular side effects including cataract, glaucoma and increased susceptibility to infections. Tacrolimus is a calcineurin inhibitor which acts mainly on T lymphocytes leading to inhibition of release of inflammatory cytokines and decreased stimulation of other inflammatory cells.<sup>4</sup> The main aim of this study is to evaluate the safety and efficacy of topical tacrolimus eye drops in the treatment of patients with ocular GVHD.

## Methods

Ten consecutive patients with ocular GVHD were included. The medical records were reviewed retrospectively. Diagnosis of chronic ocular GVHD was based on the National Institutes of Health diagnostic criteria.<sup>5</sup> We included patients who were treated with topical tacrolimus (0.01% – 0.03% twice daily) solution. We excluded patients with history of previous ocular surgery or trauma, active infection or those who are allergic to tacrolimus. Five patients were given adjunctive topical steroids (dexamethasone) for 4 to 6 weeks. The decision to use adjunctive topical steroids at the initiation of tacrolimus therapy was based on the severity of the ocular symptoms and signs. Treatment with adjunctive steroids was continued with periodic attempts to withdraw whenever possible. At the time of diagnosis of ocular GVHD all patients had already received systemic immunosuppressive therapy for their chronic GVHD manifestations. Systemic immunosuppression was unchanged in all patients and all the patients were allowed to continue their basal dry eye treatment including lubricants and punctal plugs. The outcome measures included Schirmer testing, improvement of symptoms of photophobia, ocular pain and discharge and improvement of signs of superficial punctate keratitis and conjunctival hyperemia. Clinical assessment was carried out before, during and on the last visit after treatment.

Tacrolimus eyedrops were compounded, prepared and provided to the patient as we described earlier.<sup>6</sup> The compounding of the eyedrops was carried out under sterile condition and laminar flow hood. The patients were asked not to use the tacrolimus eyedrops after 1 month from opening the bottle. They were strictly instructed to keep the bottle clean and to keep it in the refrigerator. The protocol was approved by the institutional review board of The Eye Center and The Eye Foundation for Research in Ophthalmology. The study was adherent to the tenets of the Declaration of Helsinki.

## Results

There were 9 males and 1 female patients with age range of 5 to 51 years (mean 30 years). All patients had bilateral ocular involvement. Duration of treatment ranged from 2 to 22 months (mean 6.5 months). The mean visual acuity was 20/25 before and after treatment. There was improvement of symptoms in 8 (80%) patients. Photophobia improved in 5 (100%) out of 5 patients, ocular pain in 4 (80%) out of 5 patients and mucus discharge in 2 (50%) of 4 patients. Schirmer test was measured in 8 eyes. The average wetting of the Schirmer strips after 2 minutes without anesthesia was 2 mm at presentation and 0 mm at last visit. There was improvement of superficial punctate keratitis in 8 (40%) out of the 20 eyes and conjunctival hyperemia in 12 (66%) out of 18 eyes. The response to treatment was noted to be late following initiation of therapy (average 3 weeks; range 1 to 8 weeks). Patients who were given adjunctive steroids responded faster to topical tacrolimus (average 2 weeks) compared to those without steroids (average 3 weeks).

The main side effects following topical tacrolimus use were burning sensation, redness and swollen lids. Burning sensation following topical administration occurred in 6 patients, however, it was transient and decreased with continued treatment in most of the patients. Redness occurred in 6 patients and ranged from mild to severe. Lid swelling occurred in one patient. Patients who used adjunctive topical steroids experienced less severe ocular surface adverse events.

Two patients did not respond to topical tacrolimus therapy. One patient developed severe burning and redness following application of topical tacrolimus 0.02%, the side effects were reduced with lowering the concentration of topical tacrolimus to 0.01%, however, this lower concentration was not sufficient to control the inflammation. The second patient developed redness and swelling with the use of topical tacrolimus 0.03% which were reduced with lowering the concentration to 0.02%. Similarly, this dose was not effective to control the patient symptoms and signs. The two patients did not use adjunctive steroids.

## Discussion

Topical tacrolimus has been used successfully as a steroid sparing agent in the treatment of several inflammatory ocular surface diseases.<sup>4</sup> We have reported the efficacy of topical tacrolimus in the treatment of vernal keratoconjunctivitis, Thygeson's Superficial Punctate Keratitis and in keratopathy associated with autoimmune polyglandular syndrome.<sup>7-9</sup> Although the exact pathogenesis of ocular GVHD is still unclear, the T cell mediated inflammation of the ocular surface seems to play an important role. Inhibition of T lymphocytes may therefore ameliorate ocular surface inflammation in patients with ocular GVHD. Tacrolimus is hydrophobic and has a high molecular weight with greater permeation of the conjunctiva than the cornea.<sup>4</sup> The conjunctiva is up to 20 times more permeable to lipophilic and high molecular weight drugs than the cornea. This could explain the higher efficacy of tacrolimus in patients with severe conjunctival inflammation associated with ocular GVHD.<sup>4</sup> Therefore, topical tacrolimus could be used as a sole therapeutic agent or as an adjunctive therapy in patients with ocular GVHD to minimize the duration and dose of topical steroid.

Patients with ocular GVHD usually suffer from severe symptoms that may interfere with their daily activities. Topical tacrolimus 0.03% was effective in controlling symptoms in 80% of our patients. They reported marked improvement of photophobia and ocular pain. In terms of ocular signs, there was improvement of superficial punctate keratitis in 8(40%) out of the 20 eyes and conjunctival hyperemia in 12 (66%) out of 18 eyes. The improvement of symptoms was more marked than that of signs. These findings are similar to our findings in cases of keratitis associated with Autoimmune Polyglandular Syndrome-1 where improvement of photophobia was much more marked than the keratitis.<sup>8</sup> The efficacy of topical tacrolimus for treatment of ocular GVHD has been reported earlier in previous studies. Jung et al. retrospectively studied 24 eyes of 13 patients with GVHD. Patients were treated with tacrolimus 0.02% ointment for up to 20 months.<sup>10</sup> The ocular surface inflammatory score decreased and the need for steroid treatment also decreased after initiating tacrolimus treatment. In our 5 patients that were started on combination of topical steroids and tacrolimus, topical steroids were discontinued and the patients were maintained on topical tacrolimus. Ryu and associates reported the therapeutic effect of tacrolimus 0.03% ointment in 14 eyes of 7 patients with refractory anterior segment inflammatory disease associated with GVHD.<sup>11</sup> They noted that significant reduction of inflammation initially appeared at week two for the conjunctiva and at week one for the cornea. In our study, we noted that the response to treatment appeared at an average of 3 weeks (range 1 to 8 weeks) following initiation of therapy. In our study, patients who used concomitant steroids at the initiation of tacrolimus therapy achieved faster response compared to those who did not use topical steroids concomitantly.

Abud et al. found that tacrolimus is a safe and effective therapeutic agent for the treatment of ocular manifestations of GVHD without the known ocular hypertensive effects of topical steroids.<sup>12</sup> Tam and associates demonstrated the efficacy of a 1-month use of topical 0.03% tacrolimus ointment in controlling initial inflammation in a single patient with chronic ocular GVHD.<sup>13</sup> Sanz-Marco et al reported efficacy of topical tacrolimus in treating patients with dry eye associated with GVHD.<sup>14</sup> In our study, however, topical tacrolimus did not improve dryness as measured by Schirmer test. This could be explained by several factors including: the difference in performing Schirmer test where Sanz-Marco et al tested the basal tear secretion after 5 minutes while we tested the tears after 2 minutes without anesthesia. Furthermore, patients in Sanz-Marco et al study used autologous serum which was not used in our patients. In all previous studies the time to improvement of symptoms and signs ranged from 1 to 8 weeks (table 1). In our study the time to improvement was 1 to 8 weeks (average 3 weeks). This emphasizes the importance of continuing treatment with topical tacrolimus and to avoid premature discontinuation of the drug before its action takes place. Patients with ocular GVHD are more prone to ocular surface irritation following topical use of tacrolimus because of the severe dryness and the severe superficial punctate keratopathy. However, the burning sensation is transient and subsides with continued use of the medication. Burning sensation can be minimized by reducing the concentration of topical tacrolimus until reaching the lowest effective therapeutic concentration. Furthermore, adjunctive short-term use of topical steroids may augment the anti-inflammatory effect on the ocular surface leading to more tolerance to the topical tacrolimus. Burning sensation gradually subsides with further control of inflammation and healing of superficial punctate keratopathy.

Based on our findings in this small cohort of patients we recommend initial adjunctive use of topical steroids to achieve faster response, then the patient can be maintained on topical tacrolimus alone. Our study, however, suffers from certain limitations including retrospective design with its inherent flaws and low number of patients. Further prospective, placebo controlled, randomized clinical studies are needed.

In conclusion, topical tacrolimus is a safe and effective long-term therapy in the treatment of patients with ocular GVHD. Adjunctive short-term use of topical steroids may lead to faster response to topical tacrolimus therapy. Ocular surface irritation following topical tacrolimus in patients with ocular GVHD is common; however, patients should be encouraged to continue use of topical tacrolimus as the burning sensation decreases with continued therapy.

## Declarations

### Compliance with Ethical Standards:

Samir Shoughy declares that he has no conflict of interest.

Khalid Tabbara declares that he has no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent: Retrospective non interventional series

Author contribution:

All authors substantially contributed to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work and final approval of the version to be published; and agreement to be accountable for all aspects of the work.

Funding: None

Data are available on request

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## Table

Table 1. Topical tacrolimus in ocular Graft Versus Host Disease

Authors/year	Study design	No. of eyes	Tacrolimus form	Duration of use	Time to improvement
Tam et al./2010	Case report	2	Ointment 0.03%	1 month	1 week
Ryu et al./2012	Prospective	14	Ointment 0.02%	6 months	1- 2 weeks

Sanz-Marco et al./2013	Prospective	26	Solution 0.03%	3 months	2 weeks
Jung et al./2015	Retrospective	24	Ointment 0.02%	6- 20 months	2- 8 weeks
Abud et al./2016	Prospective	48	Suspension 0.05%	10 weeks	5 weeks
Current study	Retrospective	20	Solution 0.01-0.03%	2- 22 months	1- 8 weeks