**When SLT stands for Surface “Life-belt” Treatment in a case of ocular graft-versus-host disease and glaucoma**

## Introduction

Graft versus host disease (GVHD) represents a major complication of allogenic hematological stem cell transplantation. Many different organs and tissues are affected during the course of GVHD such as the skin, liver, mouth, and the eye.[1] Ocular GVHD is a sight-threating condition that must be promptly recognized and treated. Ocular surface impairment is the most frequent manifestation of ocular GVHD and is characterized by dry eye, Meibomian gland obstruction, blepharitis and decreased tear production due to a lacrimal gland damage. Moreover, conjunctival scarring and fibrosis, as well as punctate epithelial keratitis and filamentary keratitis, can be observed.[2]

Systemic corticosteroids and immunosuppressants remain the cornerstone treatment for systemic manifestations of chronic GVHD. However, their positive effect on the ocular surface is generally not sufficient to treat the severe ocular surface inflammation caused by chronic ocular GVHD. Ocular GVHD is characterized by an increased release of proinflammatory cytokines, chemokines, surface expression of human leukocyte antigen-DR (HLA- DR), and an upregulation of intercellular adhesion molecule (ICAM)-1.[3] Topical cyclosporine 0.5% is now considered a mainstay of treatment for chronic ocular GVHD.[4] Moreover, to achieve a significant improvement in local symptoms and to reduce ocular inflammation also topical corticosteroids, lubricant eye drops, and ointments are usually administered. Warm eyelid compresses and oral tetracyclines seem able to improve Meibomian gland secretion by reducing the inflammation.

## Case presentation with illustrations and figures

A 58 years old Caucasian female complaining about severe photophobia, a foreign body sensation since three months was referred to the cornea service of our clinic. Carefully interviewed, the patient reported a history of chronic myeloid leukemia (CML), treated with allogeneic hematopoietic stem cell transplantation (HSCT) in 2016, that resulted in systemic graft-versus-host disease (GVHD).

Her past ocular history was positive for noncomplicated cataract surgery in both eyes. When interviewed, she referred a severe adverse reaction to cyclosporine. Her current medications included methylprednisolone 4 mg, azathioprine 50 mg, hydrocortisone 12 mg, bisoprolol 5mg, ramipril 5mg, pantoprazole and, a rapid-acting human insulin analog. Topical medication included Loteprednol etabonate 0.5% bid.

Schirmer's test, tear break-up time (TBUT), corneal fluorescein and conjunctival lissamine green staining, and tear film osmolarity were performed at our first consultation. The results of our evaluations revealed a severe dry eye. Symptoms of dry eye were assessed using the Ocular Surface Disease Index (OSDI). She had symptoms of ocular discomfort (OSDI = 77), severe tear deficiency in both eyes (Schirmer I OD = 2.5 mm and OS= 2 mm). TBUT was reduced in both eyes

( 3.00 s in OD and 2.00 s in OS). The tear osmolarity resulted high in both eyes (307 OD and 341 OS).

The slit-lamp examination of the eyes revealed bilateral telangiectasias of the eyelids (figure 1), subtarsal fibrosis of the upper eyelid of both eye, conjunctival fibrosis and hyperemia (figures 2 and 3), diffuse punctate epithelial erosions (PEEs) that stained positively with fluorescein (figure 4) and chronic posterior blepharitis (figure 5), compatible with a chronic ocular GVHD, classified as grade 3 ocular GVHD (NIH consensus criteria). In addition two small darkening pigmented lesions of the left upper tarsal conjunctiva were seen by everting the upper eyelid (figure 6).

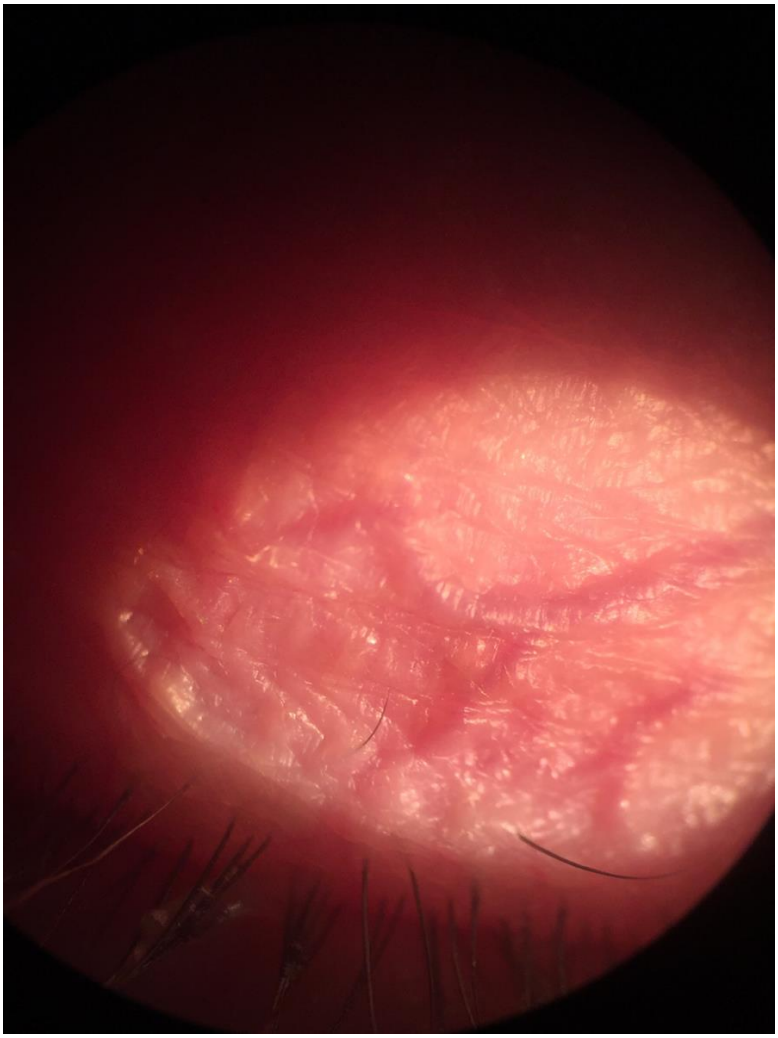

Figure 1: Telangiectasias of the eyelid.

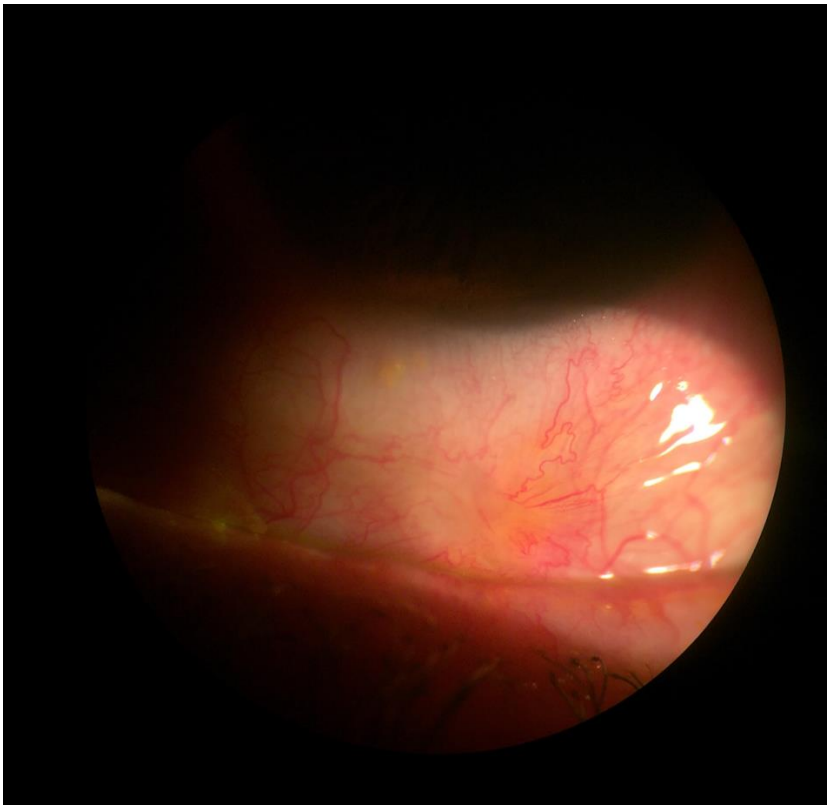

Figure 2: Conjunctival fibrosis.

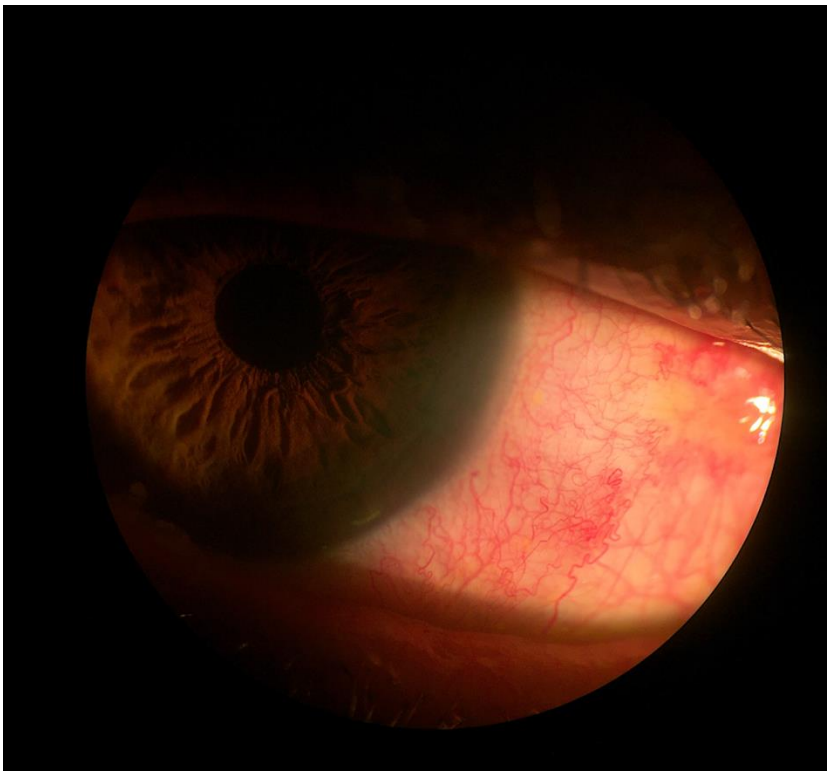

Figure 3: Conjunctival hyperemia.

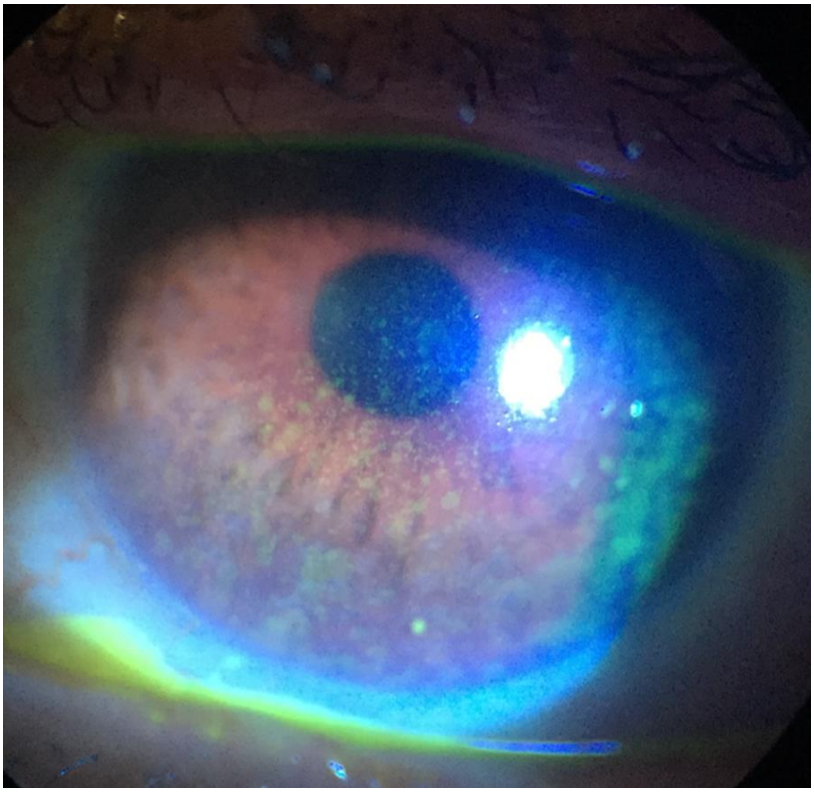

Figure 4: Diffuse punctate epithelial erosions.

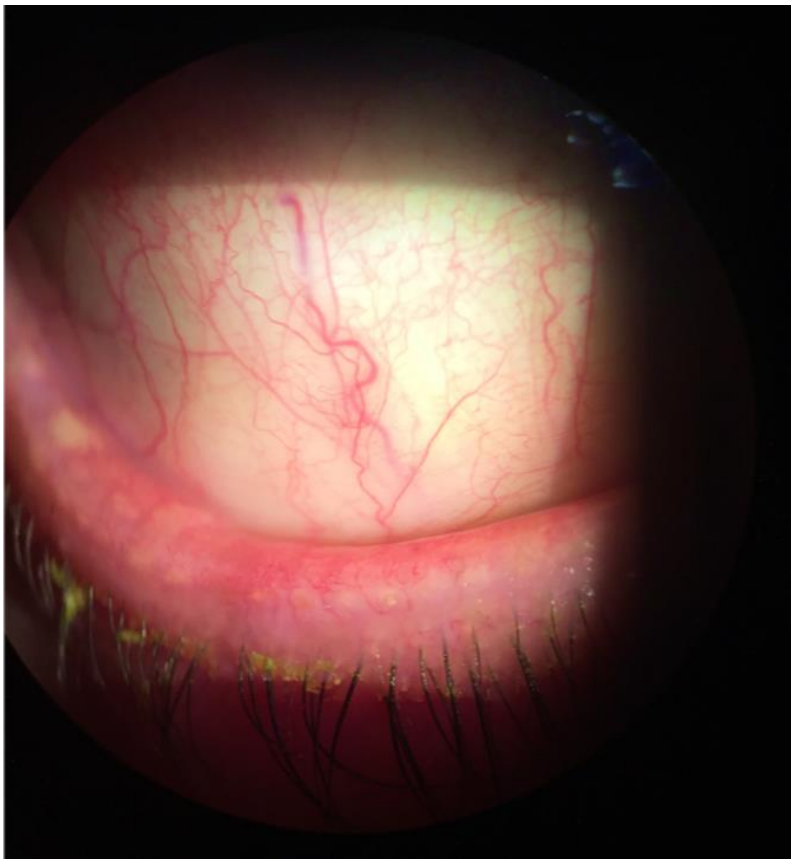

Figure 5: Chronic blepharitis with Meibomian gland disease.

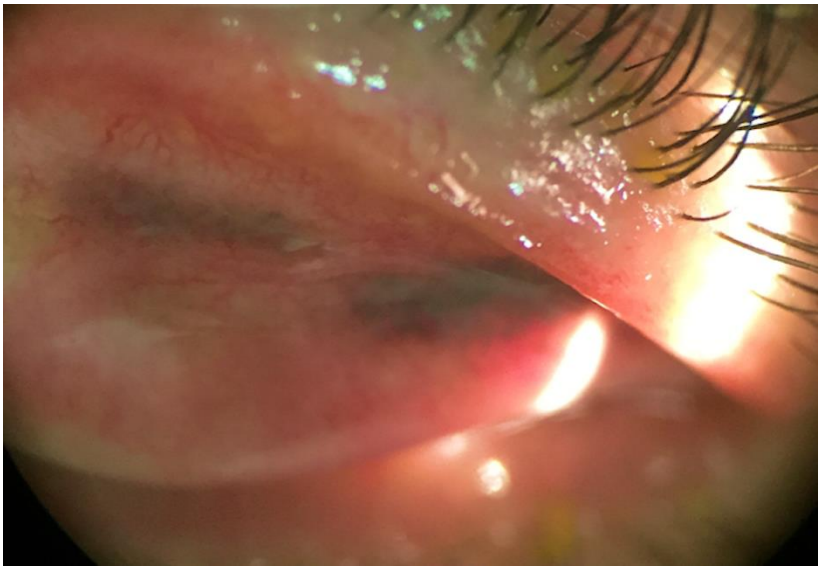

Figure 6: Blue Nevi of the tarsal conjunctiva confirmed by histology.

The patient's right-sided best correct visual acuity was 20/32 and the visual acuity on the left side was 20/50. The intraocular pressure (IOP) was very high in both eyes, 37 mm Hg (right eye) and 40 mm Hg (left eye). Clinical evaluation of the optic nerve, corneal pachymetry, and a visual field, were assessed. The central corneal thickness was 598 μm and 601 μm, respectively in the right and left eye.

Automated perimetry showed a superior nasal step in the right side and a superior arciform defect in the left eye, congruous with the optic discs' glaucomatous damage. With the aim to decrease IOP, loteprednol etabonate was tapered down slowly. An excisional biopsy stated as a Blue Nevi of the tarsal conjunctiva the histology of the pigmented lesions. Warm eyelid compresses twice a day and oral minocycline to treat the underlying Meibomian gland dysfunction (MGD) was proposed, the patient's hematologist refused the latter. At the same time, a viscous formulation consisting of hyaluronic acid, trehalose, and carbomer q4h , and azelastine 0.05% eyedrops bid, were prescribed to improve the ocular surface.

After one month, the ocular surface markedly ameliorated as well as the ocular discomfort. TBUT significantly increased and corneal fluorescein staining scores significantly decreased in both eyes. In addition, an important decrease in lissamine green staining scores was noted. No significant changes in Schirmer I test score were observed. IOP reduced, but the target pressure was not achieved yet, so a Selective Laser Trabeculoplasty (SLT) was performed. Two weeks later the IOP was 17 in the right eye and 18 in her left eye.

After eleven month, at the latest examination, the ocular surface appeared stable with almost total relief of symptoms (Figures 7 and 8).

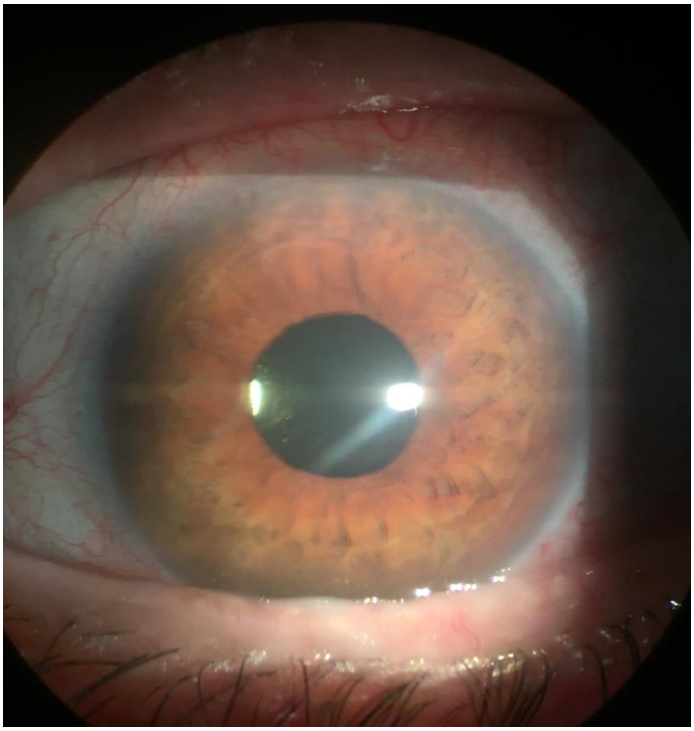

Figure 7. Ocular surface at last follow-up visit.

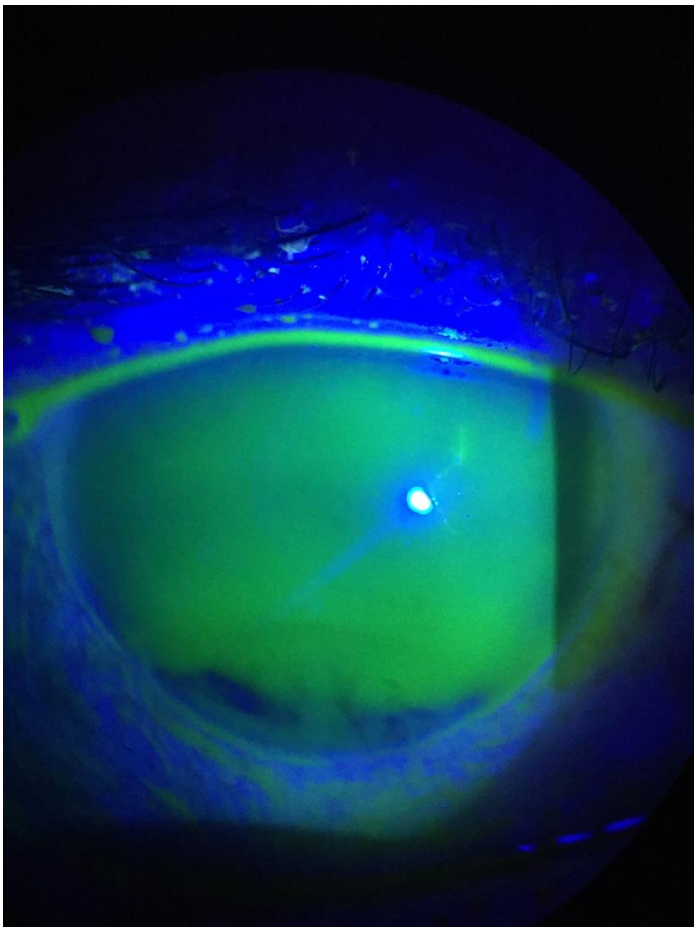

Figure 8: Staining at last follow-up visit.

## Discussion

In our case, a real challenge to control ocular surface inflammation was represented by the unfeasibility to prescribe cyclosporine, due to patient's history of severe adverse reaction, and to the necessity to reduce topical corticosteroids dependency, due to the elevated IOP. Furthermore, GVHD patients rely on many different systemic therapies and modify them could represent a risk. In our case, neither tetracycline to improve MGD, nor acetazolamide to control IOP, was permitted by the hematologist.

As first, we decided to reduce steroid eye drops because we suspected a steroid-responder ocular hypertension. Even if loteprednol etabonate has a safe IOP profile, in our patient we cannot exclude it as a cause of IOP elevation.[5] Corneal epithelium represents a mechanical barrier against absorption of topical drugs; therefore, an impaired epithelium, caused by chronic ocular surface disease, may allow increased penetration of topical corticosteroids, making these patients particularly susceptible to their adverse events, such as ocular hypertension.[6] In case of severe ocular surface disease, IOP-lowering topical drugs may exacerbate the inflammation.[7] Then, we preferred SLT as first-line treatment in order to limit the use of additional topical drugs. When SLT is not feasible or isn't able to achieve the target pressure, preservative-free topical medication should be preferred and, when more molecules are required, a fixed combination may permit to limit the number of eye drops. Moreover, SLT may be repeated if the IOP-lowering effect reduces over time. Of note, in GVHD patients, the conjunctiva is chronically inflamed and the success of bleb-forming surgical procedures such as trabeculectomy could be compromised.

To improve the ocular surface, a trehalose/hyaluronic acid/carbomer tear substitute was started. The advantage of a lachrymal substitute gel, in the author's opinion, is represented both by a lower instillation frequency needed during daytime compared to a less viscous tear substitute and by long residency on the ocular surface. Trehalose is a natural non-reducing disaccharide with two glucose molecules linked through an α, α-1,1-glucosidic bond and it seems both a bioprotectant and an osmoprotectant. It safeguards corneal cells from dehydration and high osmolarity by fortifying cell membranes and counteracting the denaturation of proteins in the lack of tears.[8]

To break the DED vicious cycle, it is mandatory to restore the tear film deficiency and to decrease ocular surface inflammation. The intercellular adhesion molecule-1 (ICAM-1) is known to play an essential role in the interaction of a variety of cells involved in immune responses and inflammation, including those prominent in ocular surface inflammation. Thus, the inhibition of ICAM-1 expression could represent a rational targeted approach in treating DED. By down-regulating ICAM-1 expression, azelastine eye drops could inhibit leukocyte adhesion and migration to the ocular surface reducing inflammation.[9,10]

## Conclusion

Ocular GVHD is a feared complication of allogenic hematological stem cell transplantation that is characterized by a sever ocular surface disease. If not treated, scarring, neovascularization or corneal perforation may occur with a critical impact on the patient's quality of life. In our case, the patient's intolerance to cyclosporine and the necessity to reduce topical steroids leads us to alternative therapies. Trehalose/hyaluronic acid permitted to ameliorate symptoms and to protect the ocular surface from the desiccating stress while azelastine was used to control the inflammation. IOP elevation is not rare in ocular GVHD patients and SLT may permit to limit the use of IOP-lowering drugs that may destabilize the ocular surface homeostasis. Optimal GVHD treatment requires a patient-tailored approach to reduce inflammation while limiting the drug's side effects. Systemic GVHD activity must always be taken into account, and collaboration with the hematologist is essential.

## References:


1. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant*. 2005;11(12):945-956. doi:10.1016/j.bbmt.2005.09.004

2. Pathak M, Diep PP, Lai X, Brinch L, Ruud E, Drolsum L. Ocular findings and ocular graft-versus-host disease after allogeneic stem cell transplantation without total body irradiation. *Bone Marrow Transplant*. 2018;53(7):863. doi:10.1038/s41409-018-0090-z

3. Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. *Surv Ophthalmol*. 2013;58(3):233-251. doi:10.1016/j.survophthal.2012.08.004

4. Malta JB, Soong HK, Shtein RM, et al. Treatment of ocular graft-versus-host disease with topical cyclosporine 0.05%. *Cornea*. 2010;29(12):1392-1396. doi:10.1097/ICO.0b013e3181e456f0

5. Cutolo CA, Barabino S, Bonzano C, Traverso CE. The Use of Topical Corticosteroids for Treatment of Dry Eye Syndrome. *Ocul Immunol Inflamm*. September 2017:1-10. doi:10.1080/09273948.2017.1341988

6. Saboo US, Amparo F, Shikari H, Dana R. Prevalence of ocular hypertension and glaucoma in patients with chronic ocular graft-versus-host disease. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 2016;254(5):923-928. doi:10.1007/s00417-016-3312-3

7. Baudouin C, Pisella PJ, Fillacier K, et al. Ocular surface inflammatory changes induced by topical antiglaucoma drugs: human and animal studies. *Ophthalmology*. 1999;106(3):556-563. doi:10.1016/S0161-6420(99)90116-1

8. Fariselli C, Giannaccare G, Fresina M, Versura P. Trehalose/hyaluronate eyedrop effects on ocular surface inflammatory markers and mucin expression in dry eye patients. *Clin Ophthalmol Auckl NZ*. 2018;12:1293-1300. doi:10.2147/OPTH.S174290

9. Ciprandi G, Buscaglia S, Catrullo A, et al. Azelastine eye drops reduce and prevent allergic conjunctival reaction and exert anti-allergic activity. *Clin Exp Allergy*. 1997;27(2):182-191. doi:10.1111/j.1365-2222.1997.tb00691.x

10. Poritz LS, Page MJ, Tilberg AF, Koltun WA. Amelioration of Graft versus Host Disease with Anti-ICAM-1 Therapy. *J Surg Res*. 1998;80(2):280-286. doi:10.1006/jsre.1998.5422