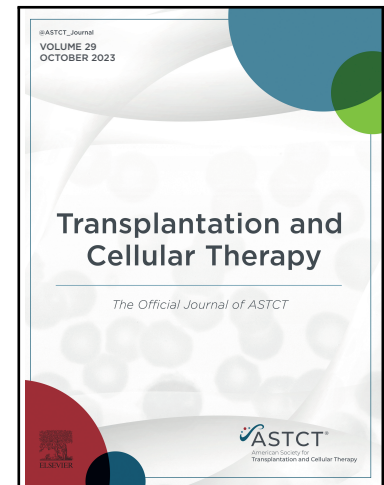


Journal Pre-proof

Understanding Ocular Graft-Versus-Host Disease to Facilitate an Integrated Multidisciplinary Approach

Pier Luigi Surico , Zhonghui K Luo

PII: S2666-6367(24)00493-7
DOI: <https://doi.org/10.1016/j.jtct.2024.06.031>
Reference: JTCT 57474



To appear in: *Transplantation and Cellular Therapy*

Received date: 26 April 2024
Accepted date: 30 June 2024

Please cite this article as: Pier Luigi Surico , Zhonghui K Luo , Understanding Ocular Graft-Versus-Host Disease to Facilitate an Integrated Multidisciplinary Approach, *Transplantation and Cellular Therapy* (2024), doi: <https://doi.org/10.1016/j.jtct.2024.06.031>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier Inc. on behalf of The American Society for Transplantation and Cellular Therapy.

Highlights

- Ocular Graft-versus-Host Disease (oGVHD) significantly impacts quality of life post-allogeneic hematopoietic stem cell transplantation (allo-HSCT) and is often underrecognized in its early stages.
- The review describes the basic concepts of pathophysiology, presentation, diagnosis and treatment options of oGVHD for all clinicians and scientists in the HSCT community.
- The review highlights the warning signs of early oGVHD development and emphasizes the importance of early recognition by all providers, promoting an integrated multidisciplinary approach.

Understanding Ocular Graft-Versus-Host Disease to Facilitate an Integrated Multidisciplinary Approach

Pier Luigi Surico^{a,b}, Zhonghui K Luo^{a,*}

^aMassachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, USA

^bCampus Bio-Medico University, Department of Ophthalmology, Rome, Italy

***CORRESPONDING AUTHOR:** Zhonghui K Luo, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA 02114, USA. E-mail: ZHONGHUI_LUO@MEEI.HARVARD.EDU

Abstract

Ocular Graft-versus-Host Disease (oGVHD) remains a challenging and potentially devastating complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT). It significantly impacts the quality of life of affected survivors, however, is often underrecognized particularly during the early stages. Targeting all providers in the HSCT community who see patients regularly and frequently for their post-allo-HSCT care, this review and opinion piece introduces the basic concepts of ocular surface pathophysiology, dissects the different stages of clinical presentation of oGVHD, explains why the current diagnostic criteria tend to capture the late disease stages, highlights the warning signs of early disease development, in hope to facilitate prompt referral of oGVHD suspects for ocular specialist care. In addition to introducing a comprehensive list of treatment options, this review emphasizes basic therapeutic strategy and options that are safe and effective to be initiated by any care provider. We believe in empowering the patients as well as the care providers beyond disciplinary boundaries, in order to provide the most cohesive and integrated care to our patients in a multidisciplinary approach.

KEY WORDS: stem cell transplantation, ocular Graft-versus-Host Disease, ocular surface disease

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for a wide range of hematological disorders, both malignant and non-malignant [1]. However, despite the transformative advances in the field in the past several decades, it is still burdened by a high incidence of complications, particularly Graft-versus-Host Disease (GVHD), which affects 30-70% of allo-HSCT survivors with high morbidity [1–3]. This review focuses on ocular GVHD (oGVHD) and hopes to serve as a diagnostic and treatment guide for non-ophthalmologic providers of post-allo-HSCT patients.

Ocular involvement occurs in all types of GVHD including acute GVHD (aGVHD), chronic GVHD (cGVHD) and overlap syndrome [4–7]. oGVHD affects over 50% of patients undergoing allo-HSCT [2,8] and even more patients with other systemic cGVHD. The incidence of oGVHD is likely underestimated due to the limited access of pre- and post-HSCT patients to ophthalmologists in most clinic settings [9]. It has been recognized that oGVHD profoundly decreases the quality of life of allo-HSCT survivors [10,11]. Just as in systemic cGVHD, donor-T-cells mediated immune response activates the cascade of inflammation and fibrosis processes that eventually leads to irreversible damage or even loss of the eye [12–16].

Dry eye disease (DED) is a hallmark (although not an equivalent) of chronic oGVHD, mostly commonly recognized from symptoms such as ocular irritation, burning, foreign body sensation, light sensitivity, redness and visual disturbances [17,18]. Ocular examination typically reveals signs of inflammation and fibrosis throughout the ocular surface that consists of the anterior ocular adnexa and cornea [19]. As a result, the new onset of dry eye, which is also called keratoconjunctivitis sicca (KCS), with evident defects in the superficial layer of the cornea are considered a diagnostic feature of oGVHD [3,20].

Involvement of the Ocular Surface in oGVHD

In contrast to the rare involvement of the deeper ocular structures such as the uvea and the retina, all structures on the ocular surface are heavily affected by oGVHD [15]. The ocular surface consists of the cornea and conjunctiva lining that are directly exposed to the outside world. The anterior ocular adnexa consists of lacrimal glands, meibomian glands, the conjunctival sac and the eyelids [21]. In hope to better explain the disease process, this review briefly describes the normal and abnormal physiology of the anterior ocular adnexa. Immune-mediate adnexa destruction directly increases the ocular surface vulnerability, therefore contributes markedly to the damage of the ocular surface broadly recognized in oGVHD.

The anterior ocular adnexa

Homeostasis of the tear film covering the ocular surface and crucial to its health is maintained by the anterior ocular adnexa. The main and accessory lacrimal glands secrete water, electrolytes, proteins, and mucins, which makes up the aqueous component of the tear film. Healthy basal lacrimation provides constant but small amounts of aqueous tears to lubricate and nourish the ocular surface in the absence of noxious stimuli [22]. The conjunctiva is a continuous lining of transparent mucous membrane that covers the eyeball (except for the cornea) and the inner layer of the eyelids. Goblet cells scattered throughout the conjunctival epithelium secrete a glycosylated mucin (among other transmembrane and secretory mucins) that turns the aqueous tears into a muco-aqueous gel. The muco-aqueous tear film carries very important functions, such as the barrier to microorganism and the lubricant to decrease friction between the eye globe and the lids. It contains many growth factors as well as factors important for innate immunity [23]. The meibomian glands (MG) are modified sebaceous glands opening to the mucocutaneous junction on each eyelid margin. Meibum, the secretion from the meibomian glands, consists of an intricate array of lipids that gets expressed by each blink to form a coating over the tear film that stabilizes it and prevents aqueous tear evaporation

[24]. Sandwiched between the keratinized skin and the mucosal conjunctiva of the eyelid are the tarsal plate, the orbicularis oculi muscles, the nasolacrimal duct drainage system, and the eyelashes, all of which play important roles in the ocular surface ecosystem. The eyelids offer the most important mechanical protection of the ocular surface and spontaneous blinking not only refreshes the tear film, but triggers meibum secretion as well [23].

The anterior adnexa in oGVHD

Preductal infiltration of the lacrimal glands by alloreactive T lymphocytes (CD4+ and CD8+) and the activation of renin-angiotensin-aldosterone system (RAAS) in oGVHD have been found to contribute to lacrimal gland fibrosis promoted by myofibroblast proliferation [25,26]. The resultant reduction or even a complete halt in tear production is considered the main reason for dry eye development. [27]

MG dysfunction is one of the most common clinical manifestations, present in approximately 50-80% of patients with oGVHD [28–30]. Chronic eyelid inflammation (blepharitis) in oGVHD adds damage to the MG [31,32]. Decreased quality and quantity of meibum destabilize the tear film, adding the evaporative component to the aqueous deficiency from the lacrimal gland damage.

cGVHD mouse models demonstrated donor T cell infiltration, endothelial injury, neovascularization, and fibroblasts activation in the MG similar to clinical presentation in humans [13,33]. Of note, some level of tear deficiency and MG dysfunction in patients can precede allo-HSCT as the result of aggressive therapies (radiation therapy, chemotherapy) and hormonal imbalances (low systemic androgens levels), rendering them more vulnerable to developing oGVHD [30,34–37].

The damage to the conjunctiva from acute and/or chronic inflammation in oGVHD causes the epithelium to slough off. Conjunctival fibrosis is often discovered in later stages [38,39]. It shares some pathologic features with lacrimal gland and MG fibrosis, such as T cell infiltration and fibroblast activation [40]. The conjunctival epithelium undergoes metaplastic changes and the goblet cells

decrease both in number and in their mucin secretory capacity, which leads to an altered mucous tear film, therefore greatly compromising the lubrication, protection and immune modulation function of the conjunctiva [40–42]. Conjunctival fibrosis can progress into severe scarring that alters the anatomy of the eyelid, like that seen in Steven-Johnsons syndrome and ocular pemphigoid. The adhesion of the bulbar and palpebral conjunctiva can dramatically shrink the surface area of the mucous membrane, obliterate the fornix (fornix foreshortening and symblepharon), pull the eyelid inward (entropion) or outward (ectropion), preventing the eyelids from fully closing (lagophthalmos), misdirecting the lashes (trichiasis and distichiasis), all of which add to the risk of exposure and mechanical trauma to the eye [5,43–45]. Additionally, the chronic inflammatory eyelid environment in oGVHD leads to the activation of enzymes (such as MMP-9) that degrade elastic fibers, resulting in eyelid laxity, which impedes normal lid function even without grossly abnormal lid appearance [46,47].

Corneal involvement in oGVHD

The cornea is a transparent, compact, and avascular multilayered tissue in the center of the ocular surface. It provides two thirds of the refractive power of the eye and contains the highest density of nerve endings of the entire human body [48]. Therefore, corneal damage leads to significant discomfort as well as serious impact on vision.

Corneal involvement in oGVHD is from both the direct immune-mediated destruction and the disturbed homeostasis from the adnexa damages described above. Donor-T-cell recruitment to the cornea and adnexa has been demonstrated in a mouse model [14]. Several studies have shown increased immune cell infiltration and activation in the corneas of oGVHD patients, particularly dendritic cells as also seen in other autoimmune diseases. Moreover, there is a neurotrophic component present in oGVHD [49,50]. The density of nerves in the sub-basal plexus of the cornea is

reduced in oGVHD patients [51]. Compromised as such, the cornea can quickly break down in the environment of a disrupted homeostasis.

The most common corneal manifestation of oGVHD is superficial punctate keratopathy, routinely visualized by fluorescein staining during an eye examination in 60 to 90% of patients [15]. Other common corneal findings include filamentary keratopathy, superior limbic keratoconjunctivitis, and recurrent epithelial defects [52–54]. In severe stages, patients with oGVHD can suffer from debilitating pain and develop irreversible vision-depriving complications such as neovascularization, corneal ulcers, and even perforation [55–57].

Clinical Presentation

The clinical presentation of oGVHD varies significantly depending on the stage of the condition, including but not limited to lacrimal gland dysfunction with DED, conjunctival hyperemia and chemosis, pseudomembranous and cicatricial conjunctivitis, MG dysfunction, corneal epitheliopathy, filaments, painful erosion, and corneal ulceration. The early recognition of oGVHD is poor [8], largely due to 1) lack of understanding how oGVHD is triggered 2) heterogeneous time of onset in relation to the HSCT 3) low accessibility to ophthalmologists with expertise in oGVHD. The current diagnostic criteria describe the dry eye condition following the ocular adnexa damage. However, the unintended implication that any symptoms and findings inconsistent with dry eyes exclude the suspicion of oGVHD has become a hindrance to early recognition. Such misconceptions are widespread among both the HSCT and ophthalmology fields, necessitating increased awareness and implementing routine pre-HSCT baseline ocular exams, as well requiring more frequent post-HSCT ocular exams when any symptom arises in order to capture early presentation.

Ocular pain and excessive tearing are the most commonly reported symptoms by patients with acute GVHD [12]. Copious mucous discharge and morning crusting without any irritation can be the warning signs of the beginning of oGVHD inflammation, new or recurrent pseudomembranous

conjunctivitis [39], which is often misdiagnosed as infectious conjunctivitis and treated ineffectively with topical antibiotics. Patients with chronic oGVHD, the most frequent form of ocular involvement, often report new or worsening dryness of the eyes, gritty and painful eyes, accompanied by irritation, redness, tearing, a sensation of foreign bodies, and even blurred vision. It has been reported to manifest most frequently between 5 and 24 months after allo-HSCT, although it can occur even sooner and be permanent [8]. It is very important to understand that the ocular symptoms occur only after the ocular adnexa have been significantly damaged, when the ocular surface can no longer maintain the minimal level of homeostasis or normal self-repair. Benign daily activities then can lead to surface trauma (microtrauma or gross trauma), which can easily get infected and/or propagate into larger area of cornea epithelium loss and stromal melting due to the absence of adnexal reserve. Although the HSCT community cares tremendously about the early diagnosis and treatment of oGVHD [2], due to the difficult and most often delayed accessibility to ophthalmology care, and the relative benign initial presentation of oGVHD, early diagnoses are rare [9,58]. The common mild early symptoms are generally insufficient to trigger an expert-level referral.

In order to facilitate early referral and diagnosis, it is important to recognize that oGVHD very often occurs at the same time or shortly after other organ GVHD[59,60] and that the events that activate the immune system can trigger oGVHD . The subtle ocular complaints can be easily buried under other organ system involvement and ignored by both the providers and patients themselves. Inquiry by system should include open-ended questions on ocular symptoms, rather than “are your eyes dry or tearing a lot?”. Lastly, oGVHD development can assume an insidious form with slow deterioration like chronic dry eyes [61]. Periodic scheduled visits with an ophthalmologist are the best form of care for early detection.

The ophthalmology clinic has specialized tools to visualize the eye with magnification and accuracy. For example: visual acuity assessment can differentiate refractive errors from pathologies not

correctable with glasses; a plethora of imaging modalities can quickly sort through other coexisting ocular issues to allow the focus to be placed back on the ocular surface. Slit-lamp examination with vital dyes can evaluate the stability of the tear film (tear breakup time test) and selectively stain epithelial damages that are otherwise invisible; Schirmer test directly measures the aqueous tear volume (although this can be done by experienced non-ophthalmologists); Cochet Bonnet esthesiometer quantifies the degree of corneal denervation; if needed, there are additional in-depth tests include meibography, tear interferometry, tear film osmolarity, and in-vivo confocal microscopy [50,62,63]. A comprehensive ophthalmologic examination provides the link between the symptoms and pathology, which is often complex.

Current Diagnostic Criteria

Strong efforts have been made by the scientific community to develop precise diagnostic criteria for oGVHD. With the aforementioned caveat in mind, two diagnostic criteria are the widely accepted and adopted currently: NIH 2014, recently updated [3,8], and the International Chronic oGVHD (ICCGVHD) consensus group diagnostic criteria, recently validated by a multicenter prospective study [64–66]. It is important to highlight that the two diagnostic criteria are complementary rather than competing as they were designed to be employed in different clinical settings. The NIH 2014 chronic GVHD diagnostic criteria were designed for the HSCT clinician who have no direct access to ocular diagnostic tools. Therefore, no formal diagnostic signs for ocular cGVHD are included. Instead, a separate ocular diagnosis of KCS is required from an ophthalmologist. According to the NIH 2014 criteria, the diagnosis of ocular cGVHD requires the presence of diagnostic or distinctive signs in other organs, reflecting its systemic approach. In contrast, the ICCGVHD system is tailored for ophthalmologists and can independently diagnose ocular chronic GVHD based on very thorough evaluations including a detailed ophthalmic examination as well as a patient questionnaire. Hopefully, a version of more unified diagnostic criteria will be developed in the near future.

NIH 2014

The NIH guidelines for diagnosing oGVHD are based on the following parameters: i) symptoms of ocular dryness and ii) a Schirmer I (without anesthesia) test score <5 mm, or the combination of i) signs of dry eye on slit lamp examination and ii) a Schirmer test score between 6 and 10 mm.

To grade the severity of oGVHD (grading 0-3), NIH criteria rely on subjective parameters, i.e., patient-reported symptoms and mainly the frequency of lubricant use [3]. (Table 1)

With this severity score, it is possible to monitor mainly the patients' symptoms, but it is difficult to determine the severity of the disease and its level of activity.

ICCGVHD

A group of expert ophthalmologists created a diagnostic and grading system for ocular involvement in GVHD in 2013. This system includes diagnostic criteria based on objective clinical parameters such as Schirmer I test, corneal fluorescein staining (CFS), Ocular Surface Disease Index (OSDI) questionnaire, and conjunctival injection. Corneal fluorescein staining highlights the compromised areas of corneal epithelial cell layer, which requires a slit lamp, therefore, is usually done in a dedicated ophthalmology clinic. Each of these parameters is associated with a score (from 0 to 3) to stage the severity of ocular surface involvement (Table 2 A). Ultimately, the final score is combined with the presence or absence of systemic GVHD to formulate the definitive, probable, or absent diagnosis of oGVHD [64] (Table 2 B).

Screening for oGVHD

All allo-HSCT survivors have an extensive medical history, even for those who had no known prior ocular pathology. The various therapeutic regimens they have been through to allow them to receive and then survive the allo-HSCT are extensive and often have ocular implications. DED and MG dysfunction have been readily found in patients prior to their allo-HSCT [30,37,67]. In addition, DED

is an high-prevalence condition, especially in the older population [68,69]. It can be a manifestation of a wide spectrum of common autoimmune and non-autoimmune systemic diseases [70–74]. After such an extensive process like allo-HSCT, patients often have trouble accurately remembering their pre-HSCT history [75]. Therefore, the pre-HSCT ocular surface history is essential to the understanding of new or worsened symptoms. A pre-HSCT screening eye examination is the best way to allow the collection of such information [30]. The majority of stem cell transplantation centers do not have an internal ophthalmic unit, therefore, it relies on the hematology-oncology providers and the primary care providers to initiate such a referral path, which would also allow patients to access immediate eye care if any complication arises after the allo-HSCT.

NIH Consensus on early diagnosis of GVHD recommends a baseline ophthalmologic specialist within a month prior to or within 3 months after the allo-HSCT and subsequent follow-up visits at the onset of any concerning eye symptoms and every 3 months for the first year and at longer intervals after [8]. The ophthalmologist should perform a complete eye exam upon the first encounter to diagnose and document all ocular conditions. Special attention to the ocular surface condition should be paid. The results of the Schirmer test, cornea sensation test, vital dye staining, lid margin health and MG expression should all be recorded diligently for future comparison. Particularly, we recommend checking the entire conjunctival surface including the superior and inferior conjunctival fornices, which requires eversion of the upper lid. In the subsequent visits, detailed ocular surface exams should be documented to track the changes if any. Severe consequences from ocular surface compromise can occur rapidly (in weeks or even days) in this special population, therefore prompt in-office examination should be offered to the patients immediately upon report or referral.

Therapeutic Management

The ideal therapeutic management is a multidisciplinary approach. GVHD often involves multiple organ systems. oGVHD is often seen along other GVHD such as oral and skin GVHD [59,60]. Prompt

communication between the HSCT team, the ophthalmologist and other specialists not only provides more context for each team to place the clinical suspicion, it promotes a concerted effort to treat the patient as a whole rather than a carrier of the individual organ systems. Systemic therapy such as immunosuppression plays an important role in organ-specific management. As recommended by the NIH cGVHD Consensus Conference [3], the goal of oGVHD therapy is to attempt to restore ocular surface homeostasis by addressing i) lubrication, ii) control of tear film volume, iii) control of tear film quality (reducing evaporation), iv) control of the inflammatory state (Table 3). Of note, currently there is no FDA-approved treatment specifically for oGVHD.

Treatment of tear deficiency

Aqueous tear deficiency affects essentially all oGVHD patients in the chronic stage and some in the acute stage. Aggressive lubrication with preservative-free (PF) artificial tears (AT) is necessary. From 4 times a day to hourly instillation may be needed to mimic the baseline continuous production of tears in a healthy ocular system. It is crucial to use PF lubricants, because the toxic effect of preservatives (e.g., benzalkonium chloride) on the ocular surface should be avoided [76]. Multidose bottles of PF-AT from many manufacturers are available as over-the-counter preparations, along with the single-use forms, which may be more convenient to use. Along with artificial tears, it may be indicated to use gel or ointment forms of PF-AT at bedtime for a prolonged effect in improving ocular discomfort. Such treatment is very safe and an excellent starting point. We recommend all non-ophthalmology providers become familiar with them and adopt a very low threshold in recommending them to the patients upon even minor ocular complaints.

To increase tear volume, the ophthalmologists can occlude the lacrimal puncta using silicone punctal plugs or collagen absorbable inserts (lasting from 90 to 180 days) [44,77–79]. Sometimes, there may be spontaneous plug loss, probably due to underlying fibrosis [80]. In these cases, thermal cautery can be performed directly at the slit lamp under topical anesthesia.

In order to increase tear production, oral secretagogue medications can be used, because of the association between oral and ocular GVHD, pilocarpine or cevimeline are already established treatment to increase saliva, it is an excellent tool for oral medicine and ophthalmology providers [81,82].

Improvement of tear film quality

Lack of high quality meibum leads to evaporative dry eyes, as discussed earlier. In fact, the hyper-evaporative state makes the DED symptoms much worse and ocular surface more easily compromised given the same tear deficiency level [21]. Blepharitis and MG dysfunction treatment with prolonged warm compresses once or twice a day, combined with eyelid hygiene [83,84] can improve meibum secretion therefore increase the quality and stability of the tear film, preventing excessive evaporation. The use of oral tetracyclines and other topical macrolides have been reported to reduce eyelid inflammation and improving meibum secretion [85]. Targeted topical steroid ointment applied specially to the eyelid margin has been shown to control blepharitis in oGVHD patients [86]. The FDA has just approved a synthetic compound, Perfluorohexyloctane for the treatment of DED in 2023. It is a physically and chemically inert liquid with low surface tension and high lipid affinity, when administered topically, it has been shown to be effective in treating MGD associated DED [87,88]. No study in the oGVHD population has been reported to date. Some newer non-invasive therapies have shown promising results in treating MGD such as intense pulsed light therapy, low-level light therapy, if and when clinically proven for oGVHD patients, can potentially become low risk treatment tools [44]. The effect of dietary supplements containing unsaturated fatty acids (omega 3 in particular) is not clear, as a clinical trial reported no benefit compared to the placebo in terms of ocular surface improvement [89]. It is worth noting that there are many over-the-counter pharmaceutical eyedrops marketed for ocular itch and redness reduction that contain antihistamines, NSAIDs, and alpha-adrenergic receptor agonists. These preparations, as well as any

other preservative-containing eye drops should be avoided. Such eyedrops are not effective and can often be harmful [44].

Trophic Support

One of the escalated options of oGVHD treatment is autologous serum tears (ASTs) [90]. The serum is extracted from the patient's own blood by centrifugation and then diluted to a concentration prescribed by the treating physician. Higher concentrations of ASTs have been shown to be more beneficial for severe ocular surface diseases [91,92]. Although no controlled trial is published to date, based on our clinical experience, ASTs can be very effective in the oGVHD population. ASTs contain numerous trophic factors that help restore ocular surface homeostasis. The neurotrophic efficacy of ASTs in promoting corneal nerve regeneration and improving corneal sensitivity, which is impaired in oGVHD patients, has been shown [93]. Although very effective, ASTs therapy has significant limitations that prevent it to be the frontline treatment: it lacks FDA approval, therefore the cost is rarely covered by medical insurance; it requires special compounding pharmacy to process freshly drawn blood every 3-6 months therefore increase the travel burden of the patients; the multi-month supply stock has to be kept frozen; the open vial in use be kept at 4 °C at all times.

At this regard, topical treatment with recombinant nerve growth factor should be considered for patients with a neurotrophic component of oGVHD [94,95]. Topical therapy with autologous platelet lysate drops has also been shown to promote corneal re-epithelialization due to the presence of platelet-derived growth factors (PDGF), with efficacy in oGVHD patients [96,97]. Given that pro-inflammatory factors can be elevated in patients with systemic GVHD, the use of serum from other sources (cord blood serum) or allogeneic serum, obtained from healthy patients, has been proposed as an alternative [98,99].

Therapeutic contact lenses

Contact lenses are also used to provide support to the ocular surface in oGVHD. Soft silicone hydrogel contact lenses are frequently used as a short-term option to facilitate ocular surface regeneration with or without a concurrently applied amniotic membrane [100–102]. Therapeutic scleral lenses, such as the Prosthetic Replacement of Ocular Surface Ecosystem (PROSE), custom-made for patients, have been effective in improving symptoms and visual acuity in oGVHD patients [58,100,103–105]. Patients who develop corneal neuropathic pain or lid anomaly (lagophthalmos, ectropion, trichiasis etc.) that predispose the ocular surface to recurrent trauma benefit even more for this therapy. The high monetary cost and time cost are the biggest obstacle to the wider application of this excellent treatment option.

Control of the inflammatory state

For inflammation control, the use of systemic immunosuppressants is often insufficient for adequate symptomatic control. However, some promising data has emerged recently [106]. Belumosudil, an oral ROCK2 inhibitor has shown a 42% overall response rate of in the eyes of patients with refractory cGVHD in the randomized phase 2 clinical trial ROCKstar [107]. Ruxolitinib, a Janus kinase 1/2 inhibitor as 2nd-line cGVHD treatment, has shown 26% ocular response rate efficacy in a phase 3 open-label, randomized clinical trial [108]. A small retrospective ophthalmological case review supported the efficacy of this agent [109]. In most cases, topical anti-inflammation agents are required at least during some part of oGVHD management. Oral and topical steroids are commonly used [45,110], although it has been shown that their efficacy is reduced in GVHD-related DED compared to non-GVHD-related DED [111]. Topical steroids, while effective, are burdened with numerous ocular side effects such as cataracts, ocular hypertension, glaucoma, epithelial defects, delayed wound healing, and an increased risk of infectious keratitis. It is advisable to use low-potency topical steroids such as fluorometholone 0.1% and loteprednol 0.5%, which have a lower incidence of the aforementioned complications [112]. It is also preferable for the patients to have regular

measurement of intraocular pressure while on oral and/or topical steroid treatment as the elevation of intraocular pressure is not otherwise detectable.

Topical cyclosporine (0.05%), a non-steroidal anti-inflammatory [113–115] has been frequently used with variable success. By inhibiting inflammatory mechanisms that occur on the ocular surface, cyclosporine leads to increased tear production and improvement in signs and symptoms of oGVHD [41,116,117]. Additionally, it has been shown that prophylactic treatment reduces the incidence and severity of oGVHD after HSCT [118–120], showing same efficacy and safety compared to topical loteprednol etabonate 0.5% [121]. However, cyclosporine can cause severe and lasting stinging sensation, therefore, the compliance is generally poor. Many other anti-inflammatory topical treatments have been investigated in the oGVHD population. The topical version of tacrolimus, one of the most used systemic immunosuppressant, both as eyedrops (0.05%) and ointment (0.03%), has demonstrated efficacy and safety in the oGVHD setting [122–124]. Lifitegrast, another drug that inhibits the recruitment of inflammatory cells to the ocular surface, has shown partial efficacy in improving GVHD-related DED [125]. Finally, topical therapy with IL-1 receptor antagonist (IL-1Ra), has been shown to be effective in reducing symptoms and epitheliopathy in patients with oGVHD refractory to standard therapies [126].

Miscellaneous therapies

Medical therapies in development

Topical tranilast, a mast cell stabilizer, has been useful in treating mild forms of GVHD-related DED [127]. Tyrosine kinase inhibitors [128] and thymosin beta 4 have also demonstrated anti-inflammatory and anti-apoptotic effects in the context of oGVHD [129]. Recombinant human DNase eye drops therapy has shown efficacy in clinical trials in patients with DED, making it a promising therapy for oGVHD patients [130]. A clinical trial on the application of 1% progesterone gel to the forehead has shown significant efficacy in reducing signs and symptoms of DED in patients with

GVHD at 10 weeks from the start of treatment, proving to be an effective new therapy for oGVHD and a novel mechanism for neuroaxis drug delivery [131]. Other recent clinical trials investigate the possible use of umbilical mesenchymal stem cell-derived exosomes (NCT04213248), and amniotic fluid eye drops (NCT03298815).

Environmental accommodation

It is well established that environment factors affect DED significantly [132]. They include low humidity, high temperature, windy conditions, poor air quality, prolonged screen time, contact lens use, high altitude, indoor heating and cooling systems, pollution, seasonal changes, and exposure to bright lights or glare. Adverse environmental conditions have been found to be a risk factor for oGVHD as well [133]. Therefore, environmental modification, if possible, should be optimized with air purifier and humidifier in the homes of oGVHD patients. In other settings, wearing moisture chambers rim-sealed goggles can reduce ocular irritation [134,135].

Behavioral modification

Ocular irritation, itchiness and foreign body sensation, along with unstable vision often prompt patients to rub their eyes, which can induce or worsen pre-existing micro- and macro-trauma [136]. It can cause subconjunctival hemorrhage, corneal abrasion or conjunctival abrasion or open wound on the periorbital skin. Rubbing also can easily dislodge punctal plugs and worsen lid-laxity. Therefore, prompt education to discourage patients from eye rubbing behavior should be incorporated into consultation by ophthalmologists and other providers alike.

Surgical interventions

Due to the poor and sometimes aberrant ocular surface healing capacity in the context of local tissue inflammation, local and systemic immunosuppression, surgical intervention should be avoided whenever possible [12]. However, patients with advanced stages of oGVHD may develop

complications such as corneal ulceration and perforation [55,137]. In these cases, in addition to corneal glueing and patch graft, amniotic membrane transplantation can be used as the first surgical step for repairing small defects and in refractory oGVHD [101,138]. Penetrating keratoplasty is a procedure with a poor prognosis in patients with oGVHD because of the high failure rate due to tissue inflammation and neovascularization in the recipient's cornea [139,140]. In cases of severe DED unresponsive to medical therapies, temporary or permanent tarsorrhaphy can be applied to promote re-epithelialization and reduce exposure [141,142].

Patients should avoid cosmetic lid procedures and refractive surgery as they increase the risk of ocular surface exposure, cornea denervation and iatrogenic trauma. Corrective lid procedures for trichiasis, entropion, ectropion, or exposure keratopathy [44,143] might be necessary but should be exercised with caution and should be performed by recognized experts. For glaucoma management, in addition to use preservative-free glaucoma topical medications, selective laser trabeculoplasty, sustained-release drug delivery systems and minimally invasive glaucoma surgery should be prioritized over traditional approaches [144].

Patients with oGVHD are more prone to develop cataracts due to the higher exposure to systemic and topical steroids. The modern cataract surgery is done via very small incisions and has been proven to be safe and effective in this population despite increased risk of complications [145,146]. Care should be taken to stabilize the ocular surface prior to the surgery if possible. Postoperative topical treatment regimen should be modified to use PF preparations of topical steroids, avoid topical NSAIDs whenever possible. Close postoperative monitoring is important to detect ocular surface compromise following the surgery and treat it promptly and aggressively, particularly in severe cases [44,147]. Whenever possible, referral to ocular surgeons with rich experiences with oGVHD for surgical procedures can decrease complication rate and improve the prognosis.

Conclusion

A multidisciplinary approach is essential for the care of allo-HSCT survivors given the complexity of their medical conditions. This piece serves as a roadmap for all care team members to understand oGVHD, in hope to promote more integrated recognition of early ocular symptoms, prompt referral and implementation of early therapies to patients' ocular health and overall quality of life.

Declaration of competing interest

The authors report no conflict of interest.

FUNDING

None

References

- [1] Copelan EA, Chojecki A, Lazarus HM, Avalos BR. Allogeneic hematopoietic cell transplantation; the current renaissance. *Blood Rev* 2019;34:34–44. <https://doi.org/10.1016/J.BLRE.2018.11.001>.
- [2] Wolff D, Radojcic V, Lafyatis R, Cinar R, Rosenstein RK, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2020 Highly morbid forms report. *Transplant Cell Ther* 2021;27:817–35. <https://doi.org/10.1016/J.JTCT.2021.06.001>.
- [3] Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 2015;21:389–401.e1. <https://doi.org/10.1016/J.BBMT.2014.12.001>.
- [4] Hessen M, Akpek EK. Ocular graft-versus-host disease. *Curr Opin Allergy Clin Immunol* 2012;12:540–7. <https://doi.org/10.1097/ACI.0b013e328357b4b9>.
- [5] Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. *Surv Ophthalmol* 2013;58:233–51. <https://doi.org/10.1016/J.SURVOPHTHAL.2012.08.004>.
- [6] Liu YC, Gau JP, Lin PY, Liu CJL, Liu CJ, Liu JH, et al. Conjunctival Acute Graft-versus-Host Disease in Adult Patients Receiving Allogeneic Hematopoietic Stem Cell Transplantation: A Cohort Study. *PLoS One* 2016;11. <https://doi.org/10.1371/JOURNAL.PONE.0167129>.
- [7] Steven P, Perez VL, Sharma A. Murine models of graft versus host disease (GVHD): Focus on ocular GVHD. *Ocul Surf* 2023;30:179–86. <https://doi.org/10.1016/J.JTOS.2023.09.006>.
- [8] Kitko CL, Pidala J, Schoemans HM, Lawitschka A, Flowers ME, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host

- Disease: IIa. The 2020 Clinical Implementation and Early Diagnosis Working Group Report. *Transplant Cell Ther* 2021;27:545–57. <https://doi.org/10.1016/J.JTCT.2021.03.033>.
- [9] Colarusso BA, Bligdon SM, Ganjei AY, Luo ZK, Kwok A, Brocks D. Ocular Graft-versus-Host Disease Underdiagnosis: A Survey Study. *Clin Ophthalmol* 2022;16:1419–26. <https://doi.org/10.2147/OPTH.S359539>.
- [10] Sun YC, Chai X, Inamoto Y, Pidala J, Martin PJ, Flowers MED, et al. Impact of Ocular Chronic Graft-versus-Host Disease on Quality of Life. *Biol Blood Marrow Transplant* 2015;21:1687–91. <https://doi.org/10.1016/J.BBMT.2015.05.020>.
- [11] Saboo US, Amparo F, Abud TB, Schaumberg DA, Dana R. Vision-Related Quality of Life in Patients with Ocular Graft-versus-Host Disease. *Ophthalmology* 2015;122:1669–74. <https://doi.org/10.1016/J.OPHTHA.2015.04.011>.
- [12] Nair S, Vanathi M, Mukhija R, Tandon R, Jain S, Ogawa Y. Update on ocular graft-versus-host disease. *Indian J Ophthalmol* 2021;69:1038–50. https://doi.org/10.4103/IJO.IJO_2016_20.
- [13] Perez VL, Mousa HM, Soifer M, Beatty C, Sarantopoulos S, Saban DR, et al. Meibomian Gland Dysfunction: A Route of Ocular Graft-Versus-Host Disease Progression That Drives a Vicious Cycle of Ocular Surface Inflammatory Damage. *Am J Ophthalmol* 2023;247:42–60. <https://doi.org/10.1016/J.AJO.2022.09.009>.
- [14] Herretes S, Ross DB, Duffort S, Barreras H, Yaohong T, Saeed AM, et al. Recruitment of Donor T Cells to the Eyes During Ocular GVHD in Recipients of MHC-Matched Allogeneic Hematopoietic Stem Cell Transplants. *Invest Ophthalmol Vis Sci* 2015;56:2348–57. <https://doi.org/10.1167/IOVS.14-15630>.
- [15] Soleimani M, Mahdavi Sharif P, Cheraqpour K, Koganti R, Masoumi A, Baharnoori SM, et al. Ocular graft-versus-host disease (oGVHD): From A to Z. *Surv Ophthalmol* 2023;68:697–712. <https://doi.org/10.1016/J.SURVOPHTHAL.2023.02.006>.
- [16] Singh RB, Cho W, Liu C, Naderi A, Surico PL, Kahale F, et al. Immunopathological mechanisms and clinical manifestations of ocular graft-versus-host disease following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2024. <https://doi.org/10.1038/S41409-024-02321-3>.
- [17] Ogawa Y, Kuwana M. Dry eye as a major complication associated with chronic graft-versus-host disease after hematopoietic stem cell transplantation. *Cornea* 2003;22. <https://doi.org/10.1097/00003226-200310001-00004>.
- [18] Gomes JAP, Azar DT, Baudouin C, Efron N, Hirayama M, Horwath-Winter J, et al. TFOS DEWS II iatrogenic report. *Ocul Surf* 2017;15:511–38. <https://doi.org/10.1016/J.JTOS.2017.05.004>.
- [19] Giannaccare G, Pellegrini M, Bernabei F, Scorgia V, Campos E. Ocular surface system alterations in ocular graft-versus-host disease: all the pieces of the complex puzzle. *Graefes Arch Clin Exp Ophthalmol* 2019;257. <https://doi.org/10.1007/S00417-019-04301-6>.
- [20] Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, 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;11:945–56. <https://doi.org/10.1016/J.BBMT.2005.09.004>.

- [21] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf* 2017;15:276–83. <https://doi.org/10.1016/j.jtos.2017.05.008>.
- [22] Meng ID, Kurose M. The role of corneal afferent neurons in regulating tears under normal and dry eye conditions. *Exp Eye Res* 2013;117:79–87. <https://doi.org/10.1016/j.EXER.2013.08.011>.
- [23] Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. *Ocular Surface* 2017;15:438–510. <https://doi.org/10.1016/j.jtos.2017.05.011>.
- [24] Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. *Invest Ophthalmol Vis Sci* 2011;52:1938–78. <https://doi.org/10.1167/IOVS.10-6997C>.
- [25] Shamloo K, Weng J, Ross C, Lee J, Alfuraih S, Totonchy J, et al. Local Renin-Angiotensin System Activation and Myofibroblast Formation in Graft Versus Host Disease-Associated Conjunctival Fibrosis. *Invest Ophthalmol Vis Sci* 2021;62:10. <https://doi.org/10.1167/IOVS.62.13.10>.
- [26] Yaguchi S, Ogawa Y, Shimmura S, Hatou S, Nakamura S, Inaba T, et al. Presence and physiologic function of the renin-angiotensin system in mouse lacrimal gland. *Invest Ophthalmol Vis Sci* 2012;53:5416–25. <https://doi.org/10.1167/IOVS.12-9891>.
- [27] Ogawa Y, Kuwana M, Yamazaki K, Mashima Y, Yamada M, Mori T, et al. Periductal area as the primary site for T-cell activation in lacrimal gland chronic graft-versus-host disease. *Invest Ophthalmol Vis Sci* 2003;44:1888–96. <https://doi.org/10.1167/IOVS.02-0699>.
- [28] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. *Ocul Surf* 2017;15:539–74. <https://doi.org/10.1016/j.jtos.2017.05.001>.
- [29] Pathak M, Diep PP, Lai X, Brinch L, Roud E, Drolsum L. Ocular findings and ocular graft-versus-host disease after allogeneic stem cell transplantation without total body irradiation. *Bone Marrow Transplant* 2018;53:863–72. <https://doi.org/10.1038/S41409-018-0090-Z>.
- [30] Giannaccare G, Bonifazi F, Sessa M, Dan E, Arpinati M, Fresina M, et al. Ocular surface analysis in hematological patients before and after allogeneic hematopoietic stem cell transplantation: implication for daily clinical practice. *Eye (Lond)* 2017;31:1417–26. <https://doi.org/10.1038/EYE.2017.78>.
- [31] Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK. The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. *Invest Ophthalmol Vis Sci* 2011;52:1994–2005. <https://doi.org/10.1167/IOVS.10-6997E>.
- [32] McCulley JP, Shine WE. Meibomian secretions in chronic blepharitis. *Adv Exp Med Biol* 1998;438:319–26. https://doi.org/10.1007/978-1-4615-5359-5_45.
- [33] Yang F, Hayashi I, Sato S, Saijo-Ban Y, Yamane M, Fukui M, et al. Eyelid blood vessel and meibomian gland changes in a sclerodermatous chronic GVHD mouse model. *Ocul Surf* 2022;26:328–41. <https://doi.org/10.1016/j.JTOS.2021.10.006>.

- [34] Eom Y, Baek S, Kim HM, Song JS. Meibomian Gland Dysfunction in Patients With Chemotherapy-Induced Lacrimal Drainage Obstruction. *Cornea* 2017;36:572–7. <https://doi.org/10.1097/ICO.0000000000001172>.
- [35] Grasso A, Di Zazzo A, Giannaccare G, Sung J, Inomata T, Shih KC, et al. Sex Hormones Related Ocular Dryness in Breast Cancer Women. *J Clin Med* 2021;10. <https://doi.org/10.3390/JCM10122620>.
- [36] Björk Y, Smith Knutsson E, Ankarberg-Lindgren C, Broman AK, Andersson I, Björkman L, et al. Androgens in women after allogeneic hematopoietic cell transplantation: impact of chronic GvHD and glucocorticoid therapy. *Bone Marrow Transplant* 2017;52:431–7. <https://doi.org/10.1038/BMT.2016.268>.
- [37] Giannaccare G, Bonifazi F, Sebastiani S, Sessa M, Pellegrini M, Arpinati M, et al. Meibomian Gland Dropout in Hematological Patients Before Hematopoietic Stem Cell Transplantation. *Cornea* 2018;37:1264–9. <https://doi.org/10.1097/ICO.0000000000001585>.
- [38] Kheirkhah A, Coco G, Satitpitakul V, Dana R. Subtarsal Fibrosis Is Associated With Ocular Surface Epitheliopathy in Graft-Versus-Host Disease. *Am J Ophthalmol* 2018;189:102–10. <https://doi.org/10.1016/j.ajophth.2018.02.020>.
- [39] Jabs DA, Wingard J, Green WR, Farmer ER, Vogelsang G, Saral R. The eye in bone marrow transplantation. III. Conjunctival graft-vs-host disease. *Arch Ophthalmol* 1989;107:1343–8. <https://doi.org/10.1001/ARCHOPHT.1989.01070020413046>.
- [40] Ogawa Y, Shimmura S, Kawakita T, Yoshida S, Kawakami Y, Tsubota K. Epithelial mesenchymal transition in human ocular chronic graft-versus-host disease. *Am J Pathol* 2009;175:2372–81. <https://doi.org/10.2353/AJPATH.2009.090318>.
- [41] Wang Y, Ogawa Y, Dogru M, Kawai M, Tatematsu Y, Uchino M, et al. Ocular surface and tear functions after topical cyclosporine treatment in dry eye patients with chronic graft-versus-host disease. *Bone Marrow Transplant* 2008;41:293–302. <https://doi.org/10.1038/SJ.BMT.1705900>.
- [42] Wang Y, Ogawa Y, Dogru M, Tatematsu Y, Uchino M, Kamo M, et al. Baseline profiles of ocular surface and tear dynamics after allogeneic hematopoietic stem cell transplantation in patients with or without chronic GVHD-related dry eye. *Bone Marrow Transplant* 2010;45:1077–83. <https://doi.org/10.1038/BMT.2009.312>.
- [43] Sivaraman KR, Jivrajka R V., Soin K, Bouchard CS, Movahedan A, Shorter E, et al. Superior Limbic Keratoconjunctivitis-like Inflammation in Patients with Chronic Graft-Versus-Host Disease. *Ocul Surf* 2016;14:393–400. <https://doi.org/10.1016/j.jtos.2016.04.003>.
- [44] Gomes JAP, Azar DT, Baudouin C, Bitton E, Chen W, Hafezi F, et al. TFOS Lifestyle: Impact of elective medications and procedures on the ocular surface. *Ocul Surf* 2023;29:331–85. <https://doi.org/10.1016/j.jtos.2023.04.011>.
- [45] Robinson MR, Lee SS, Rubin BI, Wayne AS, Pavletic SZ, Bishop MR, et al. Topical corticosteroid therapy for cicatricial conjunctivitis associated with chronic graft-versus-host disease. *Bone Marrow Transplant* 2004;33:1031–5. <https://doi.org/10.1038/SJ.BMT.1704453>.

- [46] Giannaccare G, Bernabei F, Pellegrini M, Arpinati M, Bonifazi F, Sessa M, et al. Eyelid metrics assessment in patients with chronic ocular graft versus-host disease. *Ocul Surf* 2019;17:98–103. <https://doi.org/10.1016/J.JTOS.2018.10.005>.
- [47] Nair S, Vanathi M, Mahapatra M, Seth T, Kaur J, Velpandian T, et al. Tear inflammatory mediators and protein in eyes of post allogenic hematopoietic stem cell transplant patients. *Ocul Surf* 2018;16:352–67. <https://doi.org/10.1016/J.JTOS.2018.04.007>.
- [48] DelMonte DW, Kim T. Anatomy and physiology of the cornea. *J Cataract Refract Surg* 2011;37:588–98. <https://doi.org/10.1016/J.JCRS.2010.12.037>.
- [49] Tepelus TC, Chiu GB, Maram J, Huang J, Chopra V, Sadda SVR, et al. Corneal features in ocular graft-versus-host disease by in vivo confocal microscopy. *Graefes Arch Clin Exp Ophthalmol* 2017;255:2389–97. <https://doi.org/10.1007/S00417-017-3759-X>.
- [50] Kheirkhah A, Qazi Y, Arnoldner MA, Suri K, Dana R. In Vivo Confocal Microscopy in Dry Eye Disease Associated With Chronic Graft-Versus-Host Disease. *Invest Ophthalmol Vis Sci* 2016;57:4686–91. <https://doi.org/10.1167/IOVS.16-20013>.
- [51] He J, Ogawa Y, Mukai S, Saijo-Ban Y, Kamoi M, Uchino M, et al. In Vivo Confocal Microscopy Evaluation of Ocular Surface with Graft-Versus-Host Disease-Related Dry Eye Disease. *Sci Rep* 2017;7. <https://doi.org/10.1038/s41598-017-10237-w>.
- [52] Sinha S, Singh RB, Dohlman TH, Wang M, Taketani Y, Yin J, et al. Prevalence of Persistent Corneal Epithelial Defects in Chronic Ocular Graft-Versus-Host Disease. *Am J Ophthalmol* 2020;218:296–303. <https://doi.org/10.1016/J.AJO.2020.05.035>.
- [53] Pérez RL, Pérez-Simón JA, Caballero-Velazquez T, Flores T, Carrancio S, Herrero C, et al. Limbus damage in ocular graft-versus-host disease. *Biol Blood Marrow Transplant* 2011;17:270–3. <https://doi.org/10.1016/J.BBMT.2010.08.008>.
- [54] Liu S, Peng R, Ma J, Shen Z, Hu B, Zhao Y, et al. Assessment of Corneal Epithelial Changes and Related Factors in Ocular Chronic Graft-Versus-Host Disease (GVHD) by in Vivo Confocal Microscopy. *Ocul Immunol Inflamm* 2023. <https://doi.org/10.1080/09273948.2023.2173240>.
- [55] Stevenson W, Shikari H, Saboo US, Amparo F, Dana R. Bilateral corneal ulceration in ocular graft-versus-host disease. *Clin Ophthalmol* 2013;7:2153–8. <https://doi.org/10.2147/OPTH.S51180>.
- [56] Sinha S, Singh RB, Dohlman TH, Taketani Y, Yin J, Dana R. Prevalence and Risk Factors Associated With Corneal Perforation in Chronic Ocular Graft-Versus-Host-Disease. *Cornea* 2021;40:877–82. <https://doi.org/10.1097/ICO.0000000000002526>.
- [57] Pellegrini M, Bernabei F, Barbato F, Arpinati M, Giannaccare G, Versura P, et al. Incidence, Risk Factors and Complications of Ocular Graft-Versus-Host Disease Following Hematopoietic Stem Cell Transplantation. *Am J Ophthalmol* 2021;227:25–34. <https://doi.org/10.1016/J.AJO.2021.02.022>.
- [58] Bligdon SM, Colarusso BA, Ganjei AY, Kwok A, Luo ZK, Brocks D. Scleral Lens and Prosthetic Replacement of the Ocular Surface Ecosystem Utilization in Ocular Graft-versus-Host Disease: A Survey Study. *Clin Ophthalmol* 2021;15:4829–38. <https://doi.org/10.2147/OPTH.S337824>.

- [59] Wang JCC, Teichman JC, Mustafa M, O'Donnell H, Broady R, Yeung SN. Risk factors for the development of ocular graft-versus-host disease (GVHD) dry eye syndrome in patients with chronic GVHD. *Br J Ophthalmol* 2015;99:1514–8. <https://doi.org/10.1136/BJOPHTHALMOL-2014-306438>.
- [60] Leite SC, de Castro RS, Alves M, Cunha DA, Correa MEP, da Silveira LA, et al. Risk factors and characteristics of ocular complications, and efficacy of autologous serum tears after haematopoietic progenitor cell transplantation. *Bone Marrow Transplant* 2006;38:223–7. <https://doi.org/10.1038/SJ.BMT.1705426>.
- [61] Ogawa Y, Okamoto S, Wakui M, Watanabe R, Yamada M, Yoshino M, et al. Dry eye after haematopoietic stem cell transplantation. *Br J Ophthalmol* 1999;83:1125–30. <https://doi.org/10.1136/BJO.83.10.1125>.
- [62] Engel LA, Wittig S, Bock F, Sauerbier L, Scheid C, Holtick U, et al. Meibography and meibomian gland measurements in ocular graft-versus-host disease. *Bone Marrow Transplant* 2015;50:961–7. <https://doi.org/10.1038/BMT.2015.72>.
- [63] Hosaka E, Kawamorita T, Ogasawara Y, Nakayama N, Uozato H, Shimizu K, et al. Interferometry in the evaluation of precorneal tear film thickness in dry eye. *Am J Ophthalmol* 2011;151. <https://doi.org/10.1016/J.AJO.2010.07.019>.
- [64] Ogawa Y, Kim SK, Dana R, Clayton J, Jain S, Rosenblatt MI, et al. International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: proposed diagnostic criteria for chronic GVHD (Part I). *Sci Rep* 2013;3. <https://doi.org/10.1038/SREP03419>.
- [65] Rapoport Y, Freeman T, Koyama T, Engelhardt BG, Jagasia M, Savani BN, et al. Validation of International Chronic Ocular Graft-Versus-Host Disease (GVHD) Group Diagnostic Criteria as a Chronic Ocular GVHD-Specific Metric. *Cornea* 2017;36:258–63. <https://doi.org/10.1097/ICO.0000000000001109>.
- [66] Ogawa Y, Dana R, Kim S, Jain S, Rosenblatt MI, Perez VL, et al. Multicenter prospective validation study for international chronic ocular graft-versus-host disease consensus diagnostic criteria. *Ocul Surf* 2022;26:200–8. <https://doi.org/10.1016/J.JTOS.2022.09.002>.
- [67] Giannaccare G, Bonifazi F, Sessa M, Fresina M, Arpinati M, Bandini G, et al. Dry Eye Disease Is Already Present in Hematological Patients Before Hematopoietic Stem Cell Transplantation. *Cornea* 2016;35:638–43. <https://doi.org/10.1097/ICO.0000000000000747>.
- [68] McCann P, Abraham AG, Mukhopadhyay A, Panagiotopoulou K, Chen H, Rittiphairoj T, et al. Prevalence and Incidence of Dry Eye and Meibomian Gland Dysfunction in the United States: A Systematic Review and Meta-analysis. *JAMA Ophthalmol* 2022;140:1181–92. <https://doi.org/10.1001/JAMAOPHTHALMOL.2022.4394>.
- [69] Di Zazzo A, Coassin M, Surico PL, Bonini S. Age-related ocular surface failure: A narrative review. *Exp Eye Res* 2022;219. <https://doi.org/10.1016/J.EXER.2022.109035>.
- [70] Tsubota K, Pflugfelder SC, Liu Z, Baudouin C, Kim HM, Messmer EM, et al. Defining Dry Eye from a Clinical Perspective. *Int J Mol Sci* 2020;21:1–24. <https://doi.org/10.3390/IJMS21239271>.
- [71] Qian L, Wei W. Identified risk factors for dry eye syndrome: A systematic review and meta-analysis. *PLoS One* 2022;17. <https://doi.org/10.1371/journal.pone.0271267>.

- [72] Di Zazzo A, Micera A, Surico PL, Balzamino BO, Luccarelli V, Antonini M, et al. Ocular Surface Disease as Extraesophageal Gastroesophageal Reflux Disease Manifestation: A Specific Therapeutic Strategy. *Cornea* 2023. <https://doi.org/10.1097/ICO.0000000000003329>.
- [73] Bonini S, Di Zazzo A, Surico PL, Balzamino BO, Luccarelli V, Niutta M, et al. Inflammation and Dry Eye-like Symptoms as Concomitant Manifestations of Laryngo-Pharyngeal Reflux. *Curr Eye Res* 2023;48:724–30. <https://doi.org/10.1080/02713683.2023.2207210>.
- [74] Yoo TK, Oh E. Diabetes mellitus is associated with dry eye syndrome: a meta-analysis. *Int Ophthalmol* 2019;39:2611–20. <https://doi.org/10.1007/S10792-019-01110-Y>.
- [75] Argyriou AA, Assimakopoulos K, Iconomou G, Giannakopoulou F, Kalofonos HP. Either called “chemobrain” or “chemofog,” the long-term chemotherapy-induced cognitive decline in cancer survivors is real. *J Pain Symptom Manage* 2011;41:126–39. <https://doi.org/10.1016/J.JPAINSYMMAN.2010.04.021>.
- [76] Fraunfelder FW. Corneal toxicity from topical ocular and systemic medications. *Cornea* 2006;25:1133–8. <https://doi.org/10.1097/01.ICO.0000240084.27663.FD>.
- [77] Best AL, Labetoulle M, Legrand M, M’garrech M, Barreau E, Rousseau A. Punctal and canalicular plugs: Indications, efficacy and safety. *J Fr Ophtalmol* 2019;42:e95–104. <https://doi.org/10.1016/J.JFO.2018.12.003>.
- [78] Sabti S, Halter JP, Braun Fränkl BC, Goldblum D. Punctal occlusion is safe and efficient for the treatment of keratoconjunctivitis sicca in patients with ocular GvHD. *Bone Marrow Transplant* 2012;47:981–4. <https://doi.org/10.1038/BMT.2011.205>.
- [79] Singh RB, Yung A, Coco G, Sinha S, Dohlman TH, Yin J, et al. Efficacy and retention of silicone punctal plugs for treatment of dry eye in patients with and without ocular graft-versus-host-disease. *Ocul Surf* 2020;18:731–5. <https://doi.org/10.1016/J.JTOS.2020.07.018>.
- [80] Yaguchi S, Ogawa Y, Kamoi M, Uchino M, Tatematsu Y, Ban Y, et al. Surgical management of lacrimal punctal cauterization in chronic GVHD-related dry eye with recurrent punctal plug extrusion. *Bone Marrow Transplant* 2012;47:1465–9. <https://doi.org/10.1038/BMT.2012.50>.
- [81] Felberg S, Dantas PEC, Sato EH. Oral pilocarpine for the treatment of dry eye in patients with Sjögren’s syndrome. *Arq Bras Oftalmol* 2022;85:269–76. <https://doi.org/10.5935/0004-2749.20220069>.
- [82] Ono M, Takamura E, Shinozaki K, Tsumura T, Hamano T, Yagi Y, et al. Therapeutic effect of cevimeline on dry eye in patients with Sjögren’s syndrome: A randomized, double-blind clinical study. *Am J Ophthalmol* 2004;138:6–17. <https://doi.org/10.1016/j.ajo.2004.02.010>.
- [83] Narang P, Donthineni PR, D’Souza S, Basu S. Evaporative dry eye disease due to meibomian gland dysfunction: Preferred practice pattern guidelines for diagnosis and treatment. *Indian J Ophthalmol* 2023;71:1348–56. https://doi.org/10.4103/IJO.IJO_2841_22.
- [84] Olson MC, Korb DR, Greiner J V. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye Contact Lens* 2003;29:96–9. <https://doi.org/10.1097/01.ICL.0000060998.20142.8D>.

- [85] Vernhardsdottir RR, Magno MS, Hynneklev L, Lagali N, Dartt DA, Vehof J, et al. Antibiotic treatment for dry eye disease related to meibomian gland dysfunction and blepharitis - A review. *Ocul Surf* 2022;26:211–21. <https://doi.org/10.1016/J.JTOS.2022.08.010>.
- [86] Domenech-Estarellas EA, Mamata H, Luo ZK. Targeted steroid ointment application to the lid margins in ocular graft-versus-host disease associated blepharitis treatment. *Ocul Surf* 2021;21:348–50. <https://doi.org/10.1016/J.JTOS.2020.12.002>.
- [87] Ballesteros-Sánchez A, De-Hita-Cantalejo C, Sánchez-González MC, Jansone-Langine Z, de Sotomayor MA, Culig J, et al. Perfluorohexyloctane in dry eye disease: A systematic review of its efficacy and safety as a novel therapeutic agent. *Ocul Surf* 2023;30:254–62. <https://doi.org/10.1016/J.JTOS.2023.10.001>.
- [88] Sheppard JD, Kurata F, Epitropoulos AT, Krösner S, Vittitow JL. NOV03 for Signs and Symptoms of Dry Eye Disease Associated With Meibomian Gland Dysfunction: The Randomized Phase 3 MOJAVE Study. *Am J Ophthalmol* 2023;252:265–74. <https://doi.org/10.1016/J.AJO.2023.03.008>.
- [89] Oydanich M, Maguire MG, Pistilli M, Hamrah P, Greiner J V., Lin MC, et al. Effects of Omega-3 Supplementation on Exploratory Outcomes in the Dry Eye Assessment and Management Study. *Ophthalmology* 2020;127:136–8. <https://doi.org/10.1016/J.OPHTHA.2019.07.009>.
- [90] Ogawa Y, Okamoto S, Mori T, Yamada M, Mashima Y, Watanabe R, et al. Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. *Bone Marrow Transplant* 2003;31:579–83. <https://doi.org/10.1038/SJ.BMT.1703862>.
- [91] Tahmaz V, Gehlsen U, Sauerbier L, Holtick U, Engel L, Radojska S, et al. Treatment of severe chronic ocular graft-versus-host disease using 100% autologous serum eye drops from a sealed manufacturing system: a retrospective cohort study. *Br J Ophthalmol* 2017;101:322–6. <https://doi.org/10.1136/BJOPHTHALMOL-2015-307666>.
- [92] Semeraro F, Forbice E, Braga O, Bova A, Di Salvatore A, Azzolini C. Evaluation of the efficacy of 50% autologous serum eye drops in different ocular surface pathologies. *Biomed Res Int* 2014;2014. <https://doi.org/10.1155/2014/826970>.
- [93] Carreno-Galeano JT, Johns LK, Dana R, Yin J. Autologous serum tears improve corneal nerve density and sensitivity in patients with ocular graft-versus-host disease-associated dry eye disease. *Ocul Surf* 2023;28:37–9. <https://doi.org/10.1016/J.JTOS.2023.01.004>.
- [94] Hamrah P, Massaro-Giordano M, Schanzlin D, Holland E, Berdy G, Goisis G, et al. Phase IV Multicenter, Prospective, Open-Label Clinical Trial of Cenegermin (rhNGF) for Stage 1 Neurotrophic Keratopathy (DEFENDO). *Ophthalmol Ther* 2024;13:553–70. <https://doi.org/10.1007/S40123-023-00866-Y>.
- [95] Stephen CP, Massaro-giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy A Multicenter Randomized Vehicle-Controlled Pivotal Trial 2020:14–26. <https://doi.org/10.1016/j.ophtla.2019.08.020>.
- [96] Pezzotta S, Fante C Del, Scudeller L, Cervio M, Antoniazzi ER, Perotti C. Autologous platelet lysate for treatment of refractory ocular GVHD. *Bone Marrow Transplant* 2012;47:1558–63. <https://doi.org/10.1038/BMT.2012.64>.

- [97] Sugar A, Hussain M, Chamberlain W, Dana R, Kelly DP, Ta C, et al. A Randomized Trial of Topical Fibrinogen-Depleted Human Platelet Lysate Treatment of Dry Eye Secondary to Chronic Graft-versus-Host Disease. *Ophthalmology Science* 2022;2:100176. <https://doi.org/10.1016/j.xops.2022.100176>.
- [98] Yoon KC, Jeong IY, Im SK, Park YG, Kim HJ, Choi J. Therapeutic effect of umbilical cord serum eyedrops for the treatment of dry eye associated with graft-versus-host disease. *Bone Marrow Transplant* 2007;39:231–5. <https://doi.org/10.1038/SJ.BMT.1705566>.
- [99] Na KS, Kim MS. Allogeneic serum eye drops for the treatment of dry eye patients with chronic graft-versus-host disease. *J Ocul Pharmacol Ther* 2012;28:479–83. <https://doi.org/10.1089/JOP.2012.0002>.
- [100] Sun YC, Inamoto Y, Wang RK, Lee SJ, Hung KF, Shen TT. The disposable bandage soft contact lenses therapy and anterior segment optical coherence tomography for management of ocular graft-versus-host disease. *BMC Ophthalmol* 2021;21. <https://doi.org/10.1186/S12886-021-02031-0>.
- [101] Peric Z, Skegros I, Durakovic N, Desnica L, Pulanic D, Serventi-Seiwerth R, et al. Amniotic membrane transplantation-a new approach to crossing the HLA barriers in the treatment of refractory ocular graft-versus-host disease. *Bone Marrow Transplant* 2018;53:1466–9. <https://doi.org/10.1038/S41409-018-0140-6>.
- [102] Wang Y, Jacobs DS. Role of therapeutic contact lenses in management of corneal disease. *Curr Opin Ophthalmol* 2022;33:306–10. <https://doi.org/10.1097/ICU.0000000000000859>.
- [103] Deloss KS, Le HG, Gire A, Chiu GB, Jacobs DS, Carrasquillo KG. PROSE Treatment for Ocular Chronic Graft-Versus-Host Disease as a Clinical Network Expands. *Eye Contact Lens* 2016;42:262–6. <https://doi.org/10.1097/ICL.0000000000000186>.
- [104] Magro L, Gauthier J, Richet M, Robin M, Nguyen S, Suarez F, et al. Scleral lenses for severe chronic GvHD-related keratoconjunctivitis sicca: a retrospective study by the SFGM-TC. *Bone Marrow Transplant* 2017;52:878–82. <https://doi.org/10.1038/BMT.2017.9>.
- [105] Agranat JS, Kitos NR, Jacobs DS. Prosthetic replacement of the ocular surface ecosystem: impact at 5 years. *Br J Ophthalmol* 2016;100:1171–5. <https://doi.org/10.1136/BJOPHTHALMOL-2015-307483>.
- [106] Zeiser R, Lee SJ. Three US Food and Drug Administration-approved therapies for chronic GVHD. *Blood* 2022;139:1642–5. <https://doi.org/10.1182/BLOOD.2021014448>.
- [107] Cutler C, Lee SJ, Arai S, Rotta M, Zoghi B, Lazaryan A, et al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. *Blood* 2021;138:2278–89. <https://doi.org/10.1182/BLOOD.2021012021>.
- [108] Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *N Engl J Med* 2021;385:228–38. <https://doi.org/10.1056/NEJMOA2033122>.
- [109] Sajjan S, Tibbs E, Utz M, Rapoport AP, Yared J, Dahiya S, et al. Can Janus kinase inhibition improve ocular graft versus host disease? *Ocul Surf* 2023;28:27–9. <https://doi.org/10.1016/j.jtos.2023.01.001>.

- [110] Hoyt R, Ritchie DS, Roberts AW, MacGregor L, Curtis DJ, Szer J, et al. Cyclosporin, methotrexate and prednisolone for graft-versus-host disease prophylaxis in allogeneic peripheral blood progenitor cell transplants. *Bone Marrow Transplant* 2008;41:651–8. <https://doi.org/10.1038/sj.bmt.1705955>.
- [111] Yin J, Kheirkhah A, Dohlman T, Saboo U, Dana R. Reduced Efficacy of Low-dose Topical Steroids in Dry Eye Disease Associated With Graft-versus-Host Disease. *Am J Ophthalmol* 2018;190:17–23. <https://doi.org/10.1016/j.ajoph.2018.03.024>.
- [112] Inamoto Y, Petriček I, Burns L, Chhabra S, DeFilipp Z, Hematti P, et al. Non-GVHD ocular complications after hematopoietic cell transplantation: expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. *Bone Marrow Transplant* 2019;54:648–61. <https://doi.org/10.1038/S41409-018-0339-6>.
- [113] Rao SN, Rao RD. Efficacy of topical cyclosporine 0.05% in the treatment of dry eye associated with graft versus host disease. *Cornea* 2006;25:674–8. <https://doi.org/10.1097/01.ICC.0000208813.17367.0C>.
- [114] Lelli GJ, Musch DC, Gupta A, Farjo QA, Nairus TM, Mian SI. Ophthalmic cyclosporine use in ocular GVHD. *Cornea* 2006;25:635–8. <https://doi.org/10.1097/01.ICC.0000208818.47861.1D>.
- [115] Barber LD, Pflugfelder SC, Tauber J, Foulks GN. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. *Ophthalmology* 2005;112:1790–4. <https://doi.org/10.1016/j.ophttha.2005.05.013>.
- [116] Dastjerdi MH, Hamrah P, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. *Cornea* 2009;28:1091–6. <https://doi.org/10.1097/ICO.0B013E3181A16472>.
- [117] Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Blood* 2000;96:2062–8. <https://doi.org/10.1182/BLOOD.V96.6.2062>.
- [118] Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A, et al. Treatment of ocular graft-versus-host disease with topical cyclosporine 0.05%. *Cornea* 2010;29:1392–6. <https://doi.org/10.1097/ICO.0B013E3181E456F0>.
- [119] Cantú-Rodríguez OG, Vázquez-Mellado A, González-Treviño JL, Martínez-Garza DM, Gómez-De León A, Hawing-Zarate JA, et al. Cyclosporine A for the Prevention of Ocular Graft versus Host Disease in Allogeneic Hematopoietic Stem Cell Transplant Recipients Is Safe and Feasible. *Acta Haematol* 2020;143:425–31. <https://doi.org/10.1159/000502405>.
- [120] Chun YH, Beak JU, Kim HS, Na KS. Topical cyclosporine pretreatment of ocular surface in allogeneic hematopoietic stem cell transplant recipients. *Journal of Ocular Pharmacology and Therapeutics* 2018;34:628–32. <https://doi.org/10.1089/jop.2018.0006>.
- [121] Boynton GE, Raoof D, Niziol LM, Hussain M, Mian SI. Prospective Randomized Trial Comparing Efficacy of Topical Loteprednol Etabonate 0.5% Versus Cyclosporine-A 0.05% for Treatment of Dry Eye Syndrome Following Hematopoietic Stem Cell Transplantation. *Cornea* 2015;34:725–32. <https://doi.org/10.1097/ICO.0000000000000436>.

- [122] Abud TB, Amparo F, Saboo US, Di Zazzo A, Dohlman TH, Ciolino JB, et al. A Clinical Trial Comparing the Safety and Efficacy of Topical Tacrolimus versus Methylprednisolone in Ocular Graft-versus-Host Disease. *Ophthalmology* 2016;123:1449–57. <https://doi.org/10.1016/J.OPHTHA.2016.02.044>.
- [123] Jung JW, Lee YJ, Yoon SC, Kim TI, Kim EK, Seo KY. Long-term result of maintenance treatment with tacrolimus ointment in chronic ocular graft-versus-host disease. *Am J Ophthalmol* 2015;159:519-527.e1. <https://doi.org/10.1016/J.AJO.2014.11.035>.
- [124] Tam PMK, Young AL, Cheng LL, Lam PTH. Topical 0.03% tacrolimus ointment in the management of ocular surface inflammation in chronic GVHD. *Bone Marrow Transplant* 2010;45:957–8. <https://doi.org/10.1038/BMT.2009.249>.
- [125] Chhabra S, Jerkins JH, Conto JE, Zellner K, Shah NN, Hari PN, et al. Lifitegrast ophthalmic solution for treatment of ocular chronic graft-versus-host disease. *Leuk Lymphoma* 2020;61:869–74. <https://doi.org/10.1080/10428194.2019.1695049>.
- [126] Amparo F, Dastjerdi MH, Okanobo A, Ferrari G, Smaga L, Hamrah P, et al. Topical interleukin 1 receptor antagonist for treatment of dry eye disease: a randomized clinical trial. *JAMA Ophthalmol* 2013;131:715–23. <https://doi.org/10.1001/JAMAOPHTHALMOL.2013.195>.
- [127] Ogawa Y, Dogru M, Uchino M, Tatematsu Y, Kamoi M, Yamamoto Y, et al. Topical tranilast for treatment of the early stage of mild dry eye associated with chronic GVHD. *Bone Marrow Transplant* 2010;45:565–9. <https://doi.org/10.1038/BMT.2009.173>.
- [128] Kheirikhah A, Di Zazzo A, Satitpitakul V, Fernandez M, Magilavy D, Dana R. A Pilot Randomized Trial on Safety and Efficacy of a Novel Topical Combined Inhibitor of Janus Kinase 1/3 and Spleen Tyrosine Kinase for GVHD-Associated Ocular Surface Disease. *Cornea* 2017;36:799–804. <https://doi.org/10.1097/ICO.0000000000001206>.
- [129] Sosne G, Ousler GW. Thymosin beta 4 ophthalmic solution for dry eye: a randomized, placebo-controlled, Phase II clinical trial conducted using the controlled adverse environment (CAE™) model. *Clin Ophthalmol* 2015;9:877–84. <https://doi.org/10.2147/OPTH.S80954>.
- [130] Mun C, Gulati S, Tibrewal S, Chen YF, An S, Surenkhuu B, et al. A Phase I/II Placebo-Controlled Randomized Pilot Clinical Trial of Recombinant Deoxyribonuclease (DNase) Eye Drops Use in Patients With Dry Eye Disease. *Transl Vis Sci Technol* 2019;8. <https://doi.org/10.1167/TVST.8.3.10>.
- [131] Luo ZK, Domenech-Estarellas EA, Han A, Lee D, Khatri R, Wahl JL, et al. Efficacy and Safety of 1% Progesterone Gel to the Forehead for Ocular Chronic Graft-versus-Host Disease. *Transplant Cell Ther* 2021;27:433.e1-433.e8. <https://doi.org/10.1016/J.JTCT.2021.02.008>.
- [132] Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II Epidemiology Report. *Ocul Surf* 2017;15:334–65. <https://doi.org/10.1016/J.JTOS.2017.05.003>.
- [133] Steven P, Faust C, Holtick U, Scheid C, Tahmaz V, Stern ME, et al. Adverse environmental conditions are a risk factor for ocular GvHD after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2020;55:1851–3. <https://doi.org/10.1038/S41409-020-0824-6>.

- [134] Huang T, Wang Y, Zhu Z, Wu Q, Chen D, Li Y. Moisture chamber goggles for the treatment of postoperative dry eye in patients receiving SMILE and FS-LASIK surgery. *BMC Ophthalmol* 2023;23. <https://doi.org/10.1186/S12886-023-03241-4>.
- [135] Waduthantri S, Tan CH, Fong YW, Tong L. Specialized moisture retention eyewear for evaporative dry eye. *Curr Eye Res* 2015;40:490–5. <https://doi.org/10.3109/02713683.2014.932389>.
- [136] McMonnies CW, Alharbi A, Boneham GC. Epithelial responses to rubbing-related mechanical forces. *Cornea* 2010;29:1223–31. <https://doi.org/10.1097/ICO.0B013E3181D3D660>.
- [137] Mohammadpour M, Maleki S, Hashemi H, Beheshtnejad AH. Recurrent Corneal Perforation due to Chronic Graft versus Host Disease; a Clinicopathologic Report. *J Ophthalmic Vis Res* 2016;11:108–11. <https://doi.org/10.4103/2008-322X.180705>.
- [138] Ikarashi H, Aketa N, Shimizu E, Takano Y, Kawakita T, Uchino Y, et al. Two case reports of continued progression of chronic ocular graft-versus-host disease without concurrent systemic comorbidities treated by amniotic membrane transplantation. *BMC Ophthalmol* 2021;21. <https://doi.org/10.1186/S12886-021-01925-3>.
- [139] Di Zazzo A, Kheirkhah A, Abud TB, Goyal S, Dana R. Management of high-risk corneal transplantation. *Surv Ophthalmol* 2017;62:816–27. <https://doi.org/10.1016/J.SURVOPHTHAL.2016.12.010>.
- [140] Zhu J, Inomata T, Di Zazzo A, Kitazawa K, Okumura Y, Coassin M, et al. Role of Immune Cell Diversity and Heterogeneity in Corneal Graft Survival: A Systematic Review and Meta-Analysis. *J Clin Med* 2021;10. <https://doi.org/10.3390/JCM10204667>.
- [141] Yeh PT, Hou YC, Lin WC, Wang IJ, Hu FR. Recurrent corneal perforation and acute calcareous corneal degeneration in chronic graft-versus-host disease. *J Formos Med Assoc* 2006;105:334–9. [https://doi.org/10.1016/S0929-6646\(09\)60125-X](https://doi.org/10.1016/S0929-6646(09)60125-X).
- [142] Pakarinen M, Tervo T, Tarkkanen A. Tarsorrhaphy in the treatment of persistent corneal lesions. *Acta Ophthalmol Suppl (Oxf)* 1987;182:69–73. <https://doi.org/10.1111/J.1755-3768.1987.TB02595.X>.
- [143] Tung CI. Graft versus host disease: what should the oculoplastic surgeon know? *Curr Opin Ophthalmol* 2017;28:499–504. <https://doi.org/10.1097/ICU.0000000000000400>.
- [144] Voicu L, Salim S. New strategies for the management of ocular surface disease in glaucoma patients. *Curr Opin Ophthalmol* 2021;32:134–40. <https://doi.org/10.1097/ICU.0000000000000739>.
- [145] Saboo US, Amparo F, Shikari H, Jurkunas U V., Dana R. Outcomes of phacoemulsification in patients with chronic ocular graft-versus-host disease. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2015;253:901–7. <https://doi.org/10.1007/s00417-015-2940-3>.
- [146] Gehlsen U, Faust C, Blecha C, Dietrich-Ntoukas T, Eberwein P, Issleib S, et al. Outcomes and complications of cataract surgery in patients with chronic ocular graft-versus-host-disease-a multicenter, retrospective analysis. *Graefes Arch Clin Exp Ophthalmol* 2022;260:2613–22. <https://doi.org/10.1007/S00417-022-05613-W>.

- [147] Bae SS, Iovieno A, Yeung SN. Long-term Outcomes of Cataract Surgery in Patients With Chronic Ocular Graft-Versus-Host Disease. *Cornea* 2022;41:587–92.
<https://doi.org/10.1097/ICO.0000000000002779>.

Table 1. NIH 2014 chronic GVHD consensus group criteria [3].

DIAGNOSTIC CRITERIA	Schirmer test ≤ 5 mm/5 min or Schirmer test 6-10 mm/5 min with evidence of KCS by slit-lamp examination			
SEVERITY GRADE	0	1	2	3
DE Symptoms/ lubricants daily use/ ADL	No symptoms/no lubricants/no impairment	Mild/ ≤ 3 times per day/no impairment	Moderate/ >3 times per day or punctal occlusion/ impaired (no loss of vision)	Severe/special eyeware to relieve pain/unable to work because of ocular symptoms or loss of vision caused by KCS

KCS=Keratoconjunctivitis Sicca, DE=Dry Eye, ADL=Activities of Daily Living

Table 2. International consensus group proposed diagnostic criteria (ICCGVHD) [64]

2A. Chronic oGVHD Severity [64]				
Severity Score (points)	Schirmer test (mm)	CFS (points)	OSDI (points)	Conj (points)
0	>15	0	<13	None
1	15-Nov	<2	13-22	Mild/Moderate
2	10-Jun	3-Feb	23-32	Severe
3	≤ 5	≥ 33	≥ 33	-
2B. Chronic oGVHD Diagnosis [64]				
	None (points)	Probable GVHD	Definite GVHD	
Systemic GVHD -	0-5	7-Jun	≥ 8	
Systemic GVHD +	0-3	5-Apr	≥ 6	

CFS=corneal fluorescein staining, (Grade 0 = no staining, Grade 1 = minimal staining, Grade 2 = mild/moderate staining, Grade 3 = severe staining); OSDI= Ocular Surface Disease Index; Conj=conjunctival injection

Total score (points)= None;0–4, Mild/Moderate; 5–8, Severe, 9–11.

Table 3. Summary of medications with efficacy in treatment of ocular GVHD.

Drug Name	Mode of Action	Form of Administration	Efficacy in Clinical Trials	FDA-Approved Indication
Autologous Serum Tears	Provides growth factors and anti-inflammatory proteins	Topical (eye drops)	Significantly improved tear film stability and ocular surface health in cGVHD patients [89]	Not FDA-approved
Azithromycin	Macrolide antibiotic; reduces inflammatory mediators in tears	Oral, topical (eye drops)	Improved tear production and reduced inflammation in DED linked to cGVHD [84]	Bacterial infections, off-label for ocular GVHD and meibomian gland dysfunction
Belumosudil	ROCK2 inhibitor; modulates fibrosis and inflammation	Oral	Improved ocular symptoms in 42% of patients with refractory cGVHD [103]	cGVHD after ≥ 2 treatments
Cenegermin	Recombinant human nerve growth factor; promotes nerve healing	Topical (eye drops)	Demonstrated improvement in corneal nerve health and function in patients with neurotrophic keratitis	Neurotrophic keratitis

			c keratitis [93,94]	
Cevimeline	Muscarinic agonist; stimulates tear and saliva production	Oral	Reported to improve tear production and reduce dry eye symptoms in oGVHD patients [82]	Sjögren's syndrome
Cyclosporine	Calcineurin inhibitor; reduces T-cell mediated immune response	Oral	Reduced ocular symptoms and maintaining tear film integrity maintaining tear film integrity [114,115]	Prophylaxis and treatment of GVHD
Cyclosporine (topical)	Immunomodulat or; increases tear production	Topical (eye drops)	Improved tear production in patients with reduced tear gland function due to oGVHD [41,111]	DED
Fluorometholone	Corticosteroid; reduces inflammation	Topical (eye drops)	Reduced ocular surface inflammatio n and improved symptoms in DED[107]	Inflammato ry eye conditions

Ibrutinib	BTK inhibitor; reduces B-cell and macrophage activity	Oral	Improved ocular surface disease index scores significantly in cGVHD [106]	cGVHD
Lifitegrast	LFA-1 antagonist; reduces T-cell mediated inflammation	Topical (eye drops)	Improved ocular surface and reduced symptoms of dry eye associated with oGVHD [119]	DED
Loteprednol	Corticosteroid; reduces inflammation	Topical (eye drops/ointment)	Reduced ocular inflammation with fewer side effects compared to other steroids [115]	Inflammatory eye conditions
Perfluorohexyloctane	Synthetic lubricant; forms a protective layer on the eye	Topical (eye drops)	Reduced symptoms of dryness and improved tear film stability [86,87]	DED
Pilocarpine	Muscarinic agonist; increases exocrine gland secretion	Oral	Enhanced tear secretion and alleviate dry eye symptoms in GVHD [81]	Dry mouth (off-label for dry eye)

Prednisone	Corticosteroid; suppresses inflammation and immune response	Oral	Common systemic treatment for all forms of GVHD; reduced inflammation and immune response [110]	GVHD (systemic treatment)
Ruxolitinib	JAK1/2 inhibitor; reduces inflammatory cytokine signaling	Oral	26% ocular response rate in patients treated for oGVHD [104]	Steroid-refractory cGVHD
Tacrolimus	Calcineurin inhibitor; suppresses T-cell activation	Oral, topical (eye drops/ointment)	Effective in reducing inflammation and improving tear production in oGVHD [116–118]	Prophylaxis and treatment of GVHD
Tetracycline	Antibacterial; reduces inflammation and bacterial growth	Oral	Improved symptoms of meibomian gland dysfunction and decreasing inflammation [84]	Meibomian gland dysfunction
Tranilast	Anti-allergic; inhibits release of inflammatory mediators	Oral	Reduced symptoms of allergic conjunctivitis and ocular	Allergic conjunctivitis (off-label for oGVHD)

			surface inflammatio n [121]	
--	--	--	-----------------------------------	--

FDA (Food and Drug Administration); GVHD (Graft-Versus-Host Disease); cGVHD (Chronic Graft-Versus-Host Disease); oGVHD (Ocular Graft-Versus-Host Disease); DED (Dry Eye Disease); ROCK2 (Rho-Associated Protein Kinase 2); BTK (Bruton's Tyrosine Kinase); LFA-1 (Lymphocyte Function-Associated Antigen 1); JAK1/2 (Janus Kinase 1/2)