Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-019-04301-6

REVIEW ARTICLE

Ocular surface system alterations in ocular graft-versus-host disease: all the pieces of the complex puzzle

Giuseppe Giannaccare[1] · Marco Pellegrini[1] · Federico Bernabei[1] · Vincenzo Scorcia[2] · Emilio Campos[1]

Received: 14 February 2019 / Revised: 11 March 2019 / Accepted: 20 March 2019

Abstract

Purpose Graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cells transplantation, occurring in about half of transplanted patients. This condition seems to be the result of a progressive immune-mediated damage that can involve various tissues, including the eyes. The ocular surface system is the ocular structure most frequently impaired, and dry eye disease is considered the hallmark of ocular GVHD. Given the increasing prevalence and the frequent severe involvement of the ocular surface with vision-threatening complications, ocular GVHD represents a current diagnostic and therapeutic challenge. The purpose of this literature review is to describe all the clinical manifestations occurring in the setting of ocular GVHD, and to further report the outcomes of conventional and novel therapies.

Methods A literature search about ocular GVHD was performed in PubMed, Scopus, Medline databases, and ClinicalTrials.gov as well as through the reference lists of identified publications until January 2019. We have included RCTs, prospective observational studies, prospective and retrospective cohort studies, pilot studies, and review articles.

Results Overall, 107 articles, 3 book chapters, and 6 ongoing registered clinical trials were collected and analyzed. Ocular GVHD can affect all the structures of the entire ocular surface system, including lacrimal and meibomian glands, cornea, conjunctiva, eyelids, nasolacrimal duct, and tears. Current medical treatment is mainly focused on lubrication and control of drainage, tear evaporation, and ocular surface inflammation. Surgical treatment may be necessary in severe, recalcitrant, or complicated cases. Amniotic membrane and tectonic keratoplasty can be valid options to restore the integrity of the cornea. Recently, conjunctival and limbal transplantation from the same living-related bone marrow donor has been proposed to manage both dry eye and limbal stem cell deficiency, without any risk of immunologic rejection.

Conclusion This review provides an up-to-date analysis on clinical findings and current and future management of ocular GVHD. A correct and prompt diagnosis along with an appropriate and aggressive treatment are fundamental for avoiding the occurrence of vision-threatening complications.

Keywords Ocular graft-versus-host disease · Allogeneic stem cell transplantation · Bone marrow transplantation · Dry eye · Ocular surface system

Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for both malignant and benign hematologic diseases. Nowadays, more than 45,000 HSCT procedures are carried out annually worldwide, and the number is further increasing each year [1]. Graft-versus-host disease (GVHD) is the major cause of morbidity and mortality following HSCT, and is mediated by complex interactions between donor and recipient immune systems, with donor-derived $CD4^+$ and $CD8^+$ T cell recognition of host antigens [2]. The incidence of GVHD ranges from 10 to 90% of patients undergoing HSCT [3], and is influenced by several factors related to both donor and recipient characteristics, such as the degree of donor/recipient mismatch, the source of the donor tissue and the underlying recipient disease [4–7]. Traditionally, any alloimmunity determining clinical manifestations within the first 100 days following HSCT was classified as "acute" GVHD; conversely, if this reaction was

✉ Giuseppe Giannaccare
giuseppe.giannaccare@gmail.com

[1] Ophthalmology Unit, St. Orsola-Malpighi University Hospital, University of Bologna, Via Palagi 9, 40138 Bologna, Italy

[2] Department of Ophthalmology, University of "Magna Graecia", Catanzaro, Italy

Published online: 03 April 2019

developed after this time threshold, it was classified as "chronic" GVHD [8]. However, the current National Institute of Health (NIH) Consensus Criteria redefined acute and chronic GVHD as distinct clinical syndromes, eliminating the temporal criterion to differentiate them [9]. As such, acute GVHD is defined as an immediate multi-organ inflammatory syndrome primarily affecting the skin, liver, and digestive tract. On the other hand, chronic GVHD is a pleiotropic, multi-organ syndrome characterized by tissue inflammation and fibrosis that involves multiple sites including the skin, lungs, liver, gastrointestinal tract, mouth, genitalia, and eyes.

Ocular chronic GVHD develops in 30 to 60% of patients after HSCT, and in 60 to 90% of patients with systemic GVHD [10]. Dry eye disease (DED) represents its hallmark, and may be associated with inflammatory damage and fibrosis of all the structures of the whole ocular surface system, including lacrimal and meibomian glands, cornea, conjunctiva, and eyelids [11–13]. Criteria for the diagnosis of ocular GVHD have been originally introduced, and recently updated, by the NIH [14–16]. According to these, the new onset of dry, gritty, or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; and confluent areas of punctate keratopathy are distinctive manifestations of chronic ocular GVHD. Recently, an International Consensus Group proposed new specialized criteria for the diagnosis of ocular GVHD that need to be performed by ophthalmologist and include ocular discomfort symptoms, Schirmer's test, corneal fluorescein staining, and conjunctival injection [17].

In the present review, we will summarize current evidence of ocular surface system alterations occurring in the setting of ocular GVHD. Furthermore, we will describe conventional and novel therapies for both medical and surgical management of patients with ocular GVHD.

Ocular surface system alterations

Lacrimal gland

The lacrimal gland represents one of the most susceptible organs to the damage of chronic GVHD. In this tissue, the main histopathological findings are the prominent increase of the number of $CD34^+$ stromal fibroblasts and the marked fibrosis of the glandular interstitium [18]. In addition, activated $CD4^+$ and $CD8^+$ T cells infiltrate the periductal area, and exert various effector functions, including cytotoxic effects on glandular epithelial cells and stimulation of the proliferation and activation of fibroblasts [19]. Recent evidence suggests that fibroblasts may have different sources, originating from either the local epithelial mesenchymal transition of the recipient [20], or donor-derived precursors [21]. Clinically, the severity of DED correlates with the degree of fibrotic changes, indicating that excessive extracellular matrix accumulation primarily contributes to the lacrimal gland exocrine dysfunction [18]. Traditionally, Schirmer's test is used to quantitatively measure the lacrimal gland production. Although it has been identified as the test with the greatest diagnostic sensitivity for ocular GVHD in two previous studies [22, 23], it is not specific, does not reflect the whole spectrum of the disease, and its reliability and sensitivity in diagnosing and monitoring DED is poor, particularly in milder cases [24].

Meibomian glands

Meibomian gland dysfunction (MGD) is one of the most common manifestations of ocular GVHD, with a reported prevalence of 47.8% [11]. The status and function of meibomian glands may be clinically assessed by slit-lamp examination of the lid margin. Patients with ocular GVHD have lower meibomian gland expressibility, and present lid margin abnormalities, such as vascular engorgement, plugged gland orifices, and anterior or posterior replacement of the mucocutaneous junction [25]. In addition, in vivo confocal microscopy (IVCM) has been used to detect meibomian gland impairment, with inflammatory cell infiltration, fibrotic changes, and obstruction of ducts [25]. This technique allowed detecting lower gland acinar unit density, shorter acinar diameter, and higher fibrosis grade in GVHD patients compared to HSCT recipients without DED. More recently, noncontact meibography has been introduced in the clinical practice for the rapid noninvasive examination of meibomian glands [26, 27]. Previous studies that employed this technique reported a significant meibomian gland dropout in hematological patients after HSCT, particularly in those developing ocular GVHD [28, 29]. Furthermore, the percentage of meibomian gland acinar area was shown to reflect the severity of ocular GVHD [30]. Our group demonstrated that meibomian gland impairment may occur in hematological patients already prior to HSTC, probably as the result of a multifactorial process caused by the concomitant therapies (i.e., chemo/radiotherapy) and/or the underlying disease itself with infiltration of the glands by tumor cells [31–33]. Representative images of noncontact meibography performed on the same patient, respectively, before (Fig. 1a) and 6 months after HSCT (Fig. 1b) show the significant meibomian gland dropout occurring after transplantation.

Cornea

Corneal fluorescein staining is one of the tests recommended to diagnose and grade ocular GVHD according to the International Chronic Ocular GVHD Consensus Group [17]. Superficial punctate keratopathy is the most common corneal manifestation (Fig. 2a); however, patients with more severe stages may develop corneal neovascularization (Fig. 2b), sterile corneal ulceration and even perforation (Fig. 2c) [34–36].

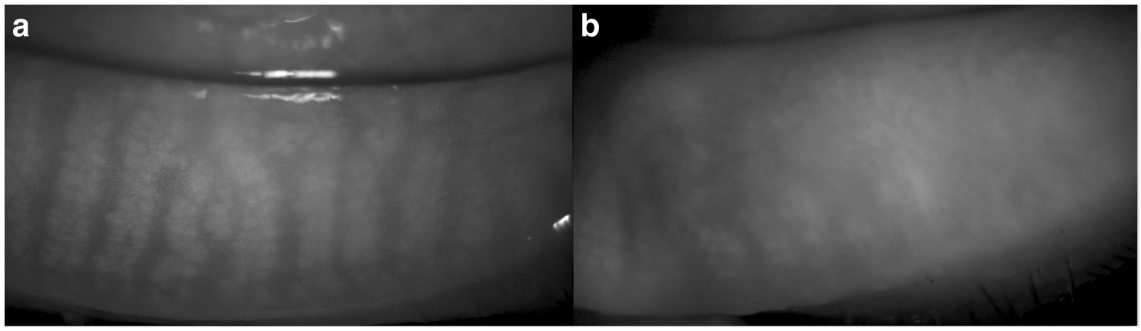

Fig. 1 Representative images of noncontact meibography performed in the same patient before (**a**) and 6 months after HSCT (**b**). Meibography revealed increased meibomian glands (MGs) dropout and loss of clarity of MGs, which appear less well demarcated compared to the surrounding tarsus

Previous IVCM studies reported significant microstructural changes in the cornea of patients with ocular GVHD, including a higher density of dendritic cells and globular immune cells, a hyper-reflective activated keratocyte network, and a lower density and higher tortuosity of sub-basal corneal nerves [37–40]. Dendritic cells act as antigen-presenting cells, and play a key role in ocular surface immune homeostasis. Thus, their increased density may be indicative of immune activation and inflammation of the ocular surface in patients with ocular GVHD. Interestingly, Kheirkhah et al. reported higher dendritic cell density in patients with DED owing to systemic immune disease (i.e., Sjögren syndrome and ocular GVHD) compared to patients with DED of other origins [37]. Recently, our group employed a fully automated IVCM analysis system to compare corneal sub-basal nerve plexus in patients with DED owing to both ocular GVHD and Sjögren syndrome and in healthy control subjects. Although overall patients with DED showed lower density of nerve fibers and branches, shorter nerve fibers and higher fiber width compared to healthy controls, no significant difference was observed between patients with ocular GVHD and Sjögren syndrome for all IVCM metrics [41]. In agreement with this observation, other studies reported no significant difference of IVCM parameters in DED patients with and without ocular GVHD after adjusting for clinical severity of dry eye [38, 39]. This suggests that the ocular surface changes observed by IVCM in ocular GVHD may be possibly reflective of the local disease severity rather than the underlying systemic process.

Conjunctiva

Conjunctival involvement in patients with ocular GVHD is typically characterized by hyperemia, chemosis, and pseudomembrane formation. In severe cases, patients may develop cicatricial conjunctivitis with fornix obliteration, symblepharon, and punctual occlusion that may mimic ocular cicatricial pemphigoid (Fig. 3a) [42, 43]. Signs of conjunctival keratinization such as squamous metaplasia and severe loss of goblet cells have been demonstrated in eyes with ocular GVHD by using conjunctival cytology [44]. Recently, superior limbic keratoconjunctivtis (SLK)-like inflammation has been detected in patients with ocular GVHD (Fig. 3b) [45]. This condition is characterized by inflammation and staining of the superior tarsal and bulbar conjunctiva, along with alteration of the superior limbal epithelium with corneal filaments. The most accepted etiopathological theory indicates that

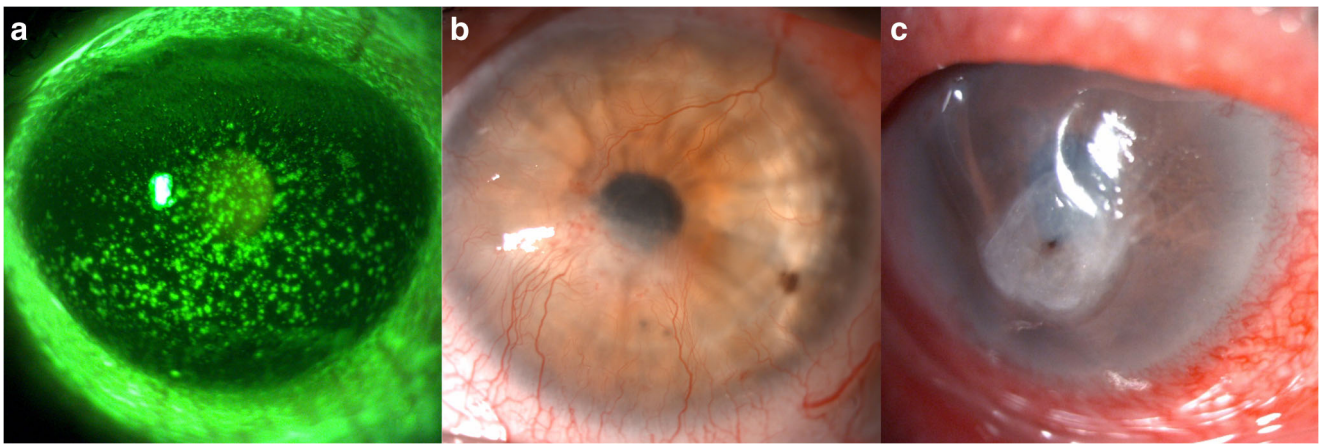

Fig. 2 Common alterations of the cornea detected in the setting of ocular graft-versus-host disease. **a** Diffuse micropunctate corneal staining after administration of 2% fluorescein dye using the blue cobalt filter and a yellow filter kit to enhance staining details. **b** Progressive superficial and deep corneal neovascularization from the whole periphery towards the center of the cornea. **c** Sterile corneal perforation

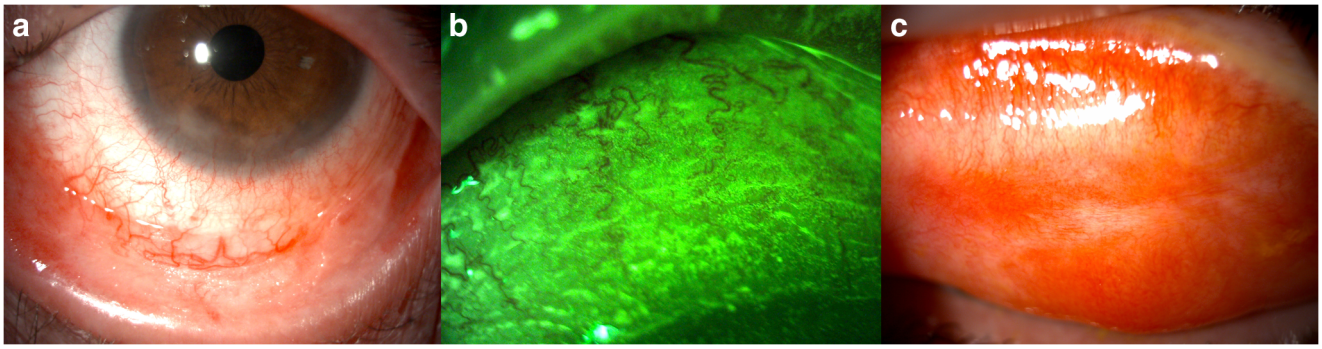

Fig. 3 Conjunctival alterations in different patients with ocular graft-versus-host disease. **a** Extensive conjunctival fibrosis with disappearance of the lower fornix. **b** Superior limbic keratoconjunctivitis after administration of 2% fluorescein dye using the blue cobalt filter and a yellow filter kit to enhance staining details. **c** Subtarsal fibrosis in the upper eyelid

increased frictional forces between the tarsal and superior palpebral conjunctiva, exacerbated by conditions like DED or tight/floppy upper eyelid, may be responsible for SLK [46]. In addition, a recent study showed that subtarsal fibrosis is present in a significant percentage of patients with chronic ocular GVHD, and is associated with a more severe ocular surface epitheliopathy (Fig. 3c) [46]. This contributory role has also been reported by previous authors for other conjunctival cicatricial diseases, like Stevens-Johnson syndrome and toxic epidermal necrolysis. Also in these cases, a strong correlation between the severity of tarsal scarring and the extent of corneal complications was observed [47]. This effect has been attributed to the blink-related microtrauma, which may cause mechanical injury as well as secondary ocular surface inflammation. The loss of conjunctival goblet cells observed in ocular GHVD may further exacerbate this process, since the mucin produced by these cells is essential for reducing frictional forces in a normal blink cycle [48].

Conjunctival involvement can be present in about 10% of cases of ocular GVHD, and represents often the spectrum of severe systemic impairment [49]. Overall, patients who exhibit this clinical picture have a worse survival prognosis compared to those who do not [50].

Eyelids

Cicatricial changes occurring in patients with ocular GVHD may affect the eyelid anatomy causing scarring, trichiasis, ectropion, entropion, and lagophthalmos [51–53]. In particular, severe entropion may lead to corneal complications, such as persistent corneal erosion and corneal clouding. In these complicated cases, surgical repair of eyelid malposition is mandatory [54–56]. Recently, our group evaluated for the first time eyelid metrics in the setting of ocular GVHD. We found that patients with ocular GVHD had a significantly higher eyelid laxity compared to control patients, even if controlled for age, sex, and degree of body mass index (Fig. 4a, b) [57]. This finding may be caused by the degradation of extracellular matrix components occurring in soft tissues due to ocular surface inflammation. In fact, it has been recently demonstrated that patients with ocular GVHD have increased tear levels of proteolytic enzymes such as matrix metalloproteinase (MMP)-9 and neutrophil elastase [58, 59]. In our study, the hyper-laxity of the upper eyelid was significantly higher in ocular GVHD patients with SLK or subtarsal fibrosis. In addition, eyelid laxity was significantly associated with ocular discomfort symptoms [57]. Therefore, testing for eyelid laxity should be recommended as part of the ocular surface examination in patients with ocular GVHD.

Nasolacrimal duct

Chronic inflammation of the epithelial and subepithelial tissues of lacrimal drainage apparatus may cause obstruction of puncta, canaliculi, or nasolacrimal duct in hematological patients after HSCT [60]. Satchi et al. showed that obstruction of the lacrimal system occurs more frequently at a proximal level, particularly in puncta and/or canaliculi [60]. In addition, Campbell and Hanada reported two cases of nasolacrimal duct obstruction in GVHD patients [61, 62]. Surgical treatment with dacryocystorhinostomy is often necessary to prevent recurrence of dacryocystitis [63]. However, it should be pointed out that the decreased tear outflow might have a protective role against DED in this kind of patient by maintaining adequate tear volume on the ocular surface. For this reason, it may be reasonable to delay as much as possible the surgical correction of lacrimal obstruction, as patients with ocular GVHD may develop a worsening of the ocular surface disease after this surgery. Therefore, it is advisable to carefully evaluate the presence and risk of DED in patients with nasolacrimal duct who are candidates for surgical correction [61, 62].

Tears

Tear proteomic analysis has become one of the most promising approaches to identify objective biomarkers that could be used as diagnostic, prognostic, and monitoring tools for both ocular and systemic diseases [64]. This field of research is

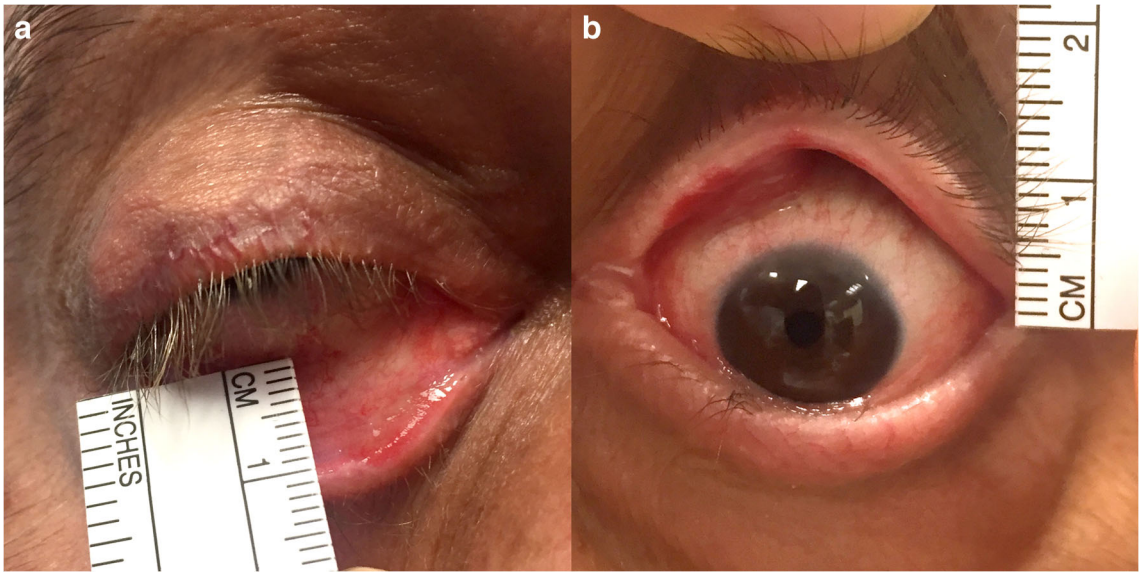

Fig. 4 Increased eyelid laxity in a representative patient with ocular graft-versus-host disease. Abnormal values for the distraction test of the lower eyelid (**a**), and for the vertical lid pull test of the upper eyelid (**b**)

particularly attractive in the setting of overall DED, due to the proximity of tears to the disease site, the lack of validated and objective diagnostic tests, and the low correlation between symptoms and objective findings. Previous studies have characterized tear cytokine profile of patients with ocular GVHD. In particular, the levels of interleukin (IL)-6 and interferon (IFN)-γ have been found to be reduced in the tears of patients with ocular GVHD [65], and the levels of IL-10, IL-6, and tumor necrosis factor-α showed significant correlation with ocular surface parameters and severity of ocular GVHD [66]. Nair et al. found a significant increase in the levels of IFN-γ, IL-6, IL-8, IL-10, IL-12AP70, IL-17A, MMP-9, and VEGF in the tears of patients with ocular GVHD, but a decrease of total tear proteins, which could be reflective of the lacrimal gland inflammation and dysfunction [59]. Cocho et al. evaluated a panel of 15 tear cytokines and found the best predictive model for ocular GVHD. If the model was based on the tear levels of IL-8/CXCL8 and inducible protein (IP)-10/CXCL10, it showed a sensitivity of 86.36% and specificity of 95.24% for reaching the diagnosis of ocular GVHD [67]. Gerber-Hollbach et al. quantified 282 tear proteins and found that 54 of them were significantly increased in the tear film of patients with GVHD compared to patients without [68]. In particular, the three most highly upregulated proteins were histone H2B, a DNA-binding protein released from dying cells; immunoglobulin gamma-1 chain C, the heavy chain constant region of immunoglobulin γ; and the intracellular scaffold protein periplakin, a protein involved in epithelial keratinization [68].

Tear hyperosmolarity is a well-recognized pathogenic mechanism of overall DED, and its measurement has been frequently reported as the single best metric to diagnose and classify the condition [69]. Previous studies have reported an increased tear osmolarity in ocular GVHD patients, and significant associations of this parameter with break-up time, Schirmer's test, ocular discomfort symptoms, and disease severity [22, 70]. In addition, the parameter has shown high sensitivity and specificity for reaching the diagnosis of ocular GVHD [71].

Medical management

The NIH chronic GVHD consensus workshop recently updated recommendations on the management ocular GVHD, and outlined four main supportive goals: (i) lubrication, (ii) control of drainage, (iii) control of evaporation, and (iv) decrease of ocular surface inflammation [72].

To lubricate the ocular surface, preservative-free tear substitutes is an essential first-line therapy in order to nourish and protect the epithelia and decrease the superficial punctate keratitis [49, 53, 73]. In a systematic review conducted on tear substitute usage in DED, no difference was observed among the various products regarding the response to treatment [74]. However, it is appropriate to avoid the use of phosphate-enriched tear substitutes in the setting of ocular GVHD, since this chemical product may favor the formation of insoluble crystalline deposits on the corneal surface when used in inflamed or damaged eyes [75].

To decrease tear drainage, either reversible punctal occlusion with silicone plug or permanent occlusion with thermal cauterization may provide additional benefits in patients with severe lacrimal gland dysfunction. Some authors have raised concern about the increased retention time of tears enriched with inflammatory cytokines that may further aggravate ocular surface inflammation. However, a recent study

demonstrated that this treatment is safe and effective in patients with ocular GVHD, allowing a significant improvement of subjective symptoms and objective findings, without increasing ocular inflammation [76].

To control tear film evaporation, eyelid hygiene with warming compresses followed by moderate to firm massage and lid margin cleansing is an effective treatment to improve meibomian gland expressibility. This procedure may also reverse to some extent meibomian gland dropout, as demonstrated in a previous meibography study [77]. Topical antibiotic ointments and systemic tetracycline derivatives may provide additional benefits if eyelid hygiene alone is not sufficient [78]. Omega-3 fatty acid supplementation may improve the quality of the meibomian gland secretions and ameliorate DED signs and symptoms [79].

To control ocular surface inflammation, topical corticosteroids are commonly used in patients with ocular GVHD. However, it has been recently demonstrated that their efficacy is reduced in patients with DED secondary to GVHD compared to those with conventional DED, even when controlling for clinical disease severity [80]. In addition, the use of topical corticosteroids is limited by the potential long-term adverse effects, including raised intraocular pressure, cataract formation, decreased wound healing, and predisposition to infection, all fearsome non-GVHD ocular complications of hematological patients [81]. Topical cyclosporine is an alternative option to control ocular surface inflammation and overcome the corticosteroids' side effects. Previous studies documented safety and effectiveness of cyclosporine eye drops in the treatment of ocular GVHD [82–84]. Additionally, Malta et al. demonstrated that initiation of cyclosporine 0.05% eye drops therapy already prior to HSCT was able to decrease the incidence and severity of ocular GVHD after transplantation [85]. Another randomized controlled trial compared the prophylactic treatment with topical loteprednol etabonate 0.5% and cyclosporine 0.05% started 1 month prior to HSCT, and showed that both drugs were similarly safe and effective in the prevention and treatment of GVHD-related DED [86]. Recently, topical tacrolimus 0.05% has been studied in a double-masked, randomized trial that showed its effectiveness in reducing local inflammation [87].

The prosthetic replacement of the ocular surface ecosystem (BostonSight PROSE, Boston Foundation for Sight, Needham, MA) employing customized scleral contact lenses has been evaluated in patients with ocular GVHD. These lenses, which act by creating a liquid reservoir between the lens itself and the cornea that hydrates and protects the corneal epithelium, have been shown to be effective in alleviating symptoms of DED and improving ocular surface integrity or appearance in patients with ocular GVHD. [88–91].

An additional goal of ocular GVHD management may be achieved by the use of blood-derived eye drops, thanks to their content of epitheliotrophic and neurotrophic factors. These biological eye drops can be obtained either from patients' own blood (i.e., autologous serum) or from donors (i.e., cord blood serum), and contain a mixture of growth factors, cytokines, and vitamins that play a key role in corneal homeostasis and wound healing [92]. Ogawa et al. investigated for the first time the use of 20% autologous serum eye drops in the treatment of ocular GVHD, and reported an improvement of dry eye symptoms, ocular surface staining, and break-up time [93]. The rationale of serum eye drops dilution is the reduction of the potentially anti-proliferative effect of transforming growth factor-beta. Other authors used also undiluted autologous serum eye drops, reporting good efficacy and no detrimental effects [94]. However, autologous serum therapy may be contraindicated in patients with poor venous access or coexisting systemic diseases, such as anemia and blood dyscrasia. In addition, the serum of patients with ocular GVHD may contain elevated levels of pro-inflammatory cytokines that may be harmful if delivered to the eye [95]. Therefore, the use of allogeneic peripheral serum obtained from healthy donors has been proposed as a viable alternative, particularly in these subtypes of patients [96, 97]. A study of Na and Kim reported a significant improvement of dry eye signs and symptoms in patients with ocular GVHD after 4 weeks of treatment with 20% allogeneic serum eye drops [96, 97]. Cord blood serum is another type of homologous serum collected from mothers during vaginal or cesarean delivery that contains higher levels of growth factors compared to peripheral blood serum [98]. Yoon et al. reported a significant amelioration of dry eye symptoms, corneal epitheliopathy, tear film stability, and corneal sensitivity in patients with ocular GVHD after 2-month treatment with cord blood serum eye drops, as well as the maintenance of the improvement for 6 months after treatment [99].

Surgical management

Patients with severe ocular GVHD are at risk for developing serious vision-threatening complications such as corneal ulceration and perforation. Amniotic membrane transplantation may be useful in patients with non-healing corneal epithelial defects to promote epithelialization, suppress inflammation, and reduce subsequent scarring [100]. Although this treatment may be also considered in cases of small corneal perforations, it is often non-resolutive, and usually a further surgery is required [36]. Tectonic keratoplasty is a safer approach to restore the integrity of the eye. However, corneal transplantation is characterized by an overall poor prognosis in patients who present a dry, inflamed, and vascularized recipient bed [101].

Limbal stem cell transplantation (LSCT) is an effective technique to treat limbal stem cell deficiency (LSCD), and restore the damaged corneal surface in severe ocular surface diseases. Allogeneic LSCT is the treatment of choice for

Table 1 Registered clinical trials about ocular graft-versus-host disease

Trial number	Title	Phase	Start date	Status	Location	Primary outcomes	Design	Treatment regimen
NCT00102583	Cyclosporine implant for oGVHD	Phase 1	October 2004	Completed	- Rockville Pike, Bethesda, MD, USA	- Schirmer's test - Corneal staining - BCVA - OSDI - TFBUT	Four participants Randomized	- Subconjunctival cyclosporine implant
NCT03414645	Topical fibrinogen-depleted human platelet lysate in patients with dry eye secondary to graft vs. host disease	Phase 1/2	May 2018	Recruiting	- Ann Arbor, MI, USA - Portland, OR, USA	- Ocular adverse events - Systemic adverse events - Corneal staining - OSDI - VAS	Sixty participants Randomized Multicenter Double-masked Placebo-controlled	- CAM-101 10% fibrinogen-depleted human platelet lysate QID for 42 days - CAM-101 30% fibrinogen-depleted human platelet lysate QID for 42 days - Placebo ophthalmic solution QID for 42 days
NCT02702518	rhDNase eye drops in patients with oGVHD	Phase 1/2	April 2016	Recruiting	Chicago, IL, USA	- Corneal staining score	Seventy-two participants Randomized Double-masked Placebo-Controlled	- rhDNase I 0.1% ophthalmic solution QID for 8 weeks - Placebo ophthalmic solution QID for 8 weeks
NCT02975557	Brimonidine eye drops for treatment of oGVHD	Phase 1/2	May 2016	Terminated	Chicago, IL, USA	- OSDI - Schirmer's test - Bulbar redness - Lid margin vascularization - Clinical and subjective global assessment	Fifteen participants Double-masked Single-Center Placebo-controlled	- Brimonidine 0.15% eye drops BID for 12 weeks - Brimonidine 0.075% eye drops, BID for 12 weeks - Placebo ophthalmic solution BID for 12 weeks
NCT01393132	Comparative study of thymosin beta 4 eye drops vs. vehicle in the treatment of severe dry eye	Phase 2	March 2011	Completed	Southfield, MI, USA	- Ocular adverse events - Corneal fluorescein staining - OSDI - TFBUT	Nine participants Randomized	- Preservative-free, sterile eye drop solution Tβ4 into each eye six times daily for 28 days - Vehicle control, BID for 12 weeks six times daily for 28 days
NCT03591874	Study of brimonidine tartrate nanoemulsion eye drops in patients with oGVHD	Phase 3	September 2018	Recruiting	- Los Angeles, CA, USA - Rochester, NY, USA - Durham, NC, USA - Columbus, OH, USA - Philadelphia, PA, USA - Nashville, TN, USA - Houston, Texas, USA	- Bulbar redness - VAS - SANDE	Sixty participants Double-masked Placebo-controlled Multicenter	- Brimonidine tartrate nanoemulsion ophthalmic solution BID for 12 weeks - Placebo ophthalmic solution BID for 12 weeks

oGVHD ocular graft-versus-host disease, *OSDI* ocular surface disease index, *VAS* visual analogue scale, *QID* quater in die, *BID* bis in die, *TFBUT* tear film break-up time, *SANDE* symptom assessment in dry eye

patients with bilateral diseases such as ocular GVHD. In vitro amplification/cultivation of corneal epithelial progenitor cells allows minimizing the size of the limbal biopsy, thus reducing the risk of iatrogenic LSCD in the donor eye [102]. However, allografts carry a significant risk of immunologic rejection, and therefore require long-term systemic immunosuppression [103]. In order to overcome this drawback, Meller et al. described the successful transplantation of limbal epithelial cells derived from the same bone marrow donor in an eye with severe GVHD [104]. The rationale for this procedure is based on the Starzl's hypothesis that bone marrow transplantation induces chimerism and consequent tolerance to tissue transplanted from the same donor at the same or later time [105]. Busin et al. transplanted limbal epithelial cells and conjunctival tissue from the same bone marrow donor in four eyes of two patients with severe GVHD [106]. Systemic immunosuppression was not necessary at any stage of the procedure, and fluorescence in situ hybridization demonstrated the survival of transplanted tissue in the recipient bed 1 year after the procedure. By using this novel approach, the additional transplantation of the conjunctiva provides the benefit of treating goblet cell loss and mucin deficiency, thus ameliorating dry eye signs and symptoms [107].

Novel therapies

Different registered clinical trials about novel treatment options for ocular GVHD are currently ongoing (Table 1).

As explained above, cyclosporine eye drops represent a valid option in the treatment of oGVHD, given its efficacy in decreasing the number of activated T cells at the ocular surface [108]. A randomized trial is currently evaluating a sustained-release subconjunctival cyclosporine implant, which bypasses the epithelial barriers in order to increase the concentrations of the drug in the lacrimal gland.

A randomized, multicenter, and double-masked trial is studying the efficacy of a fibrinogen-depleted standardized platelet lysate for improving signs and symptoms of ocular GVHD. This standardized product is obtained using pooled human platelet lysates collected from qualified healthy donors. The manufacturing process depletes pooled human platelet lysates of fibrinogen, and the final product contains higher levels of nutritive and regenerative components compared to other blood-derived products as well as healthy tear film.

A randomized, double-masked, placebo-controlled trial is evaluating the tolerability and preliminary efficacy of rhDNase I eye drops. Extracellular DNA (eDNA) is released by neutrophils following specific intracellular pathways as a part of the innate immune response, possibly contributing to the promotion of chronic inflammation at the ocular surface. RhDNase I eye drops seem to be able to clear eDNA from the ocular surface, and consequently to reduce the inflammatory reaction.

A randomized clinical trial is investigating the effects of thymosin beta 4 that is a naturally occurring polypeptide acting as a corneal modulator. This molecule has anti-inflammatory and anti-apoptotic properties, promoting healing and rapid re-epithelialization, and allowing the maintenance of a smooth and regular ocular surface [109].

Two randomized, placebo-controlled, and double-masked trials are evaluating the safety and efficacy of brimonidine solution in the context of ocular GVHD. This is a $\alpha 2$ adrenergic agonist, commonly used in glaucoma treatment, able to improve the proliferation and survival of epithelial cells of the human meibomian glands [110].

Open issues

Recently, ocular surface impairment has been documented in hematological patients already before HSCT. In fact, DED signs and symptoms as well as morphological changes of meibomian glands detected by infrared meibography have been demonstrated in a large percentage of patients already prior to HSCT [28, 31, 33]. This novel evidence opens up new perspectives, not only for the proper diagnosis and classification of ocular GVHD, but also for a deeper knowledge on the pathophysiological mechanisms of the disease. Therefore, the need for distinguishing between "conventional pre-existing dry eye" and "dry eye due to active ocular chronic GVHD" was recently pointed out by the International chronic Ocular Graft-Versus-Host Disease Consensus Group [17], the German-Austrian-Swiss Consensus Conference [14], and the 2014 updated NIH Consensus Conference [16]. Prospective studies with comprehensive baseline pre-HSCT ophthalmological evaluation are desirable to identify the actual prevalence of ocular GVHD, and to determine if early treatment of pre-existing DED as well as GVHD prophylaxis could influence its rate and severity after HSCT.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Copelan EA (2006) Hematopoietic stem-cell transplantation. N Engl J Med 354:1813–1826
2. Milosevic S, Bachnick B, Karim K et al (2010) Identification of MHC II-restricted minor histocompatibility antigens after HLA-identical stem-cell transplantation. Transplantation 90:1030–1035

3. Ferrara JL, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373:1550–1561
4. Vigorito AC, Azevedo WM, Marques JF et al (1998) A randomised, prospective comparison of allogeneic bone marrow and peripheral blood progenitor cell transplantation in the treatment of haematological malignancies. Bone Marrow Transplant 22:1145–1151
5. Powles R, Mehta J, Kulkarni S et al (2000) Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: a randomised trial. Lancet 355:1231–1237
6. Arora M, Klein JP, Weisdorf DJ, Hassebroek A et al (2011) Chronic GVHD risk score: a center for international blood and marrow transplant research analysis. Blood 117:6714–6720
7. Jagasia M, Arora M, Flowers ME et al (2012) Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood 119:296–307
8. Shulman HM, Sullivan KM, Weiden PL et al (1980) Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 69:204–217
9. Pavletic SZ, Vogelsang GB, Lee SJ (2015) 2014 National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: preface to the series. Biol Blood Marrow Transpl 21:387–388
10. Jacobs R, Tran U, Chen H et al (2012) Prevalence and risk factors associated with development of ocular GVHD defined by NIH consensus criteria. Bone Marrow Transplant 47:1470–1473
11. Ogawa Y, Okamoto S, Wakui M et al (1999) Dry eye after haematopoietic stem cell transplantation. Br J Ophthalmol 83: 1125–1130
12. Ogawa Y, Kuwana M (2003) Dry eye as a major complication associated with chronic graft-versus-host disease after hematopoietic stem cell transplantation. Cornea 22:19–27
13. Gomes JAP, Azar DT, Baudouin C (2017) TFOS DEWS II iatrogenic report. Ocul Surf 15:511–538
14. Dietrich-Ntoukas T, Cursiefen C et al (2012) Diagnosis and treatment of ocular chronic graft-versus-host disease: report from the German-Austrian-Swiss Consensus Conference on Clinical Practice in Chronic GVHD. Cornea 31:299–310
15. Filipovich AH, Weisdorf D, Pavletic S et al (2005) 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 11:945–956
16. Jagasia MH, Greinix HT, Arora M et al (2015) 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 21:389–401
17. Ogawa Y, Kim SK, Dana R, Clayton J, Jain S, Rosenblatt MI et al (2013) International chronic ocular graft-versus-host disease (GVHD) consensus group: proposed diagnostic criteria for chronic GVHD (part I). Sci Rep 3:3419
18. Ogawa Y, Yamazaki K, Kuwana M et al (2001) A significant role of stromal fibroblasts in rapidly progressive dry eye in patients with chronic GVHD. Invest Ophthalmol Vis Sci 42:111–119
19. Ogawa Y, Kuwana M, Yamazaki K et al (2003) Periductal area as the primary site for T-cell activation in lacrimal gland chronic graft-versus-host disease. Invest Ophthalmol Vis Sci 44:1888–1896
20. Ogawa Y, Shimmura S, Dogru M, Tsubota K (2010) Immune processes and pathogenic fibrosis in ocular chronic graft-versus-host disease and clinical manifestations after allogeneic hematopoietic stem cell transplantation. Cornea 29:68–77
21. Ogawa Y, Kodama H, Kameyama K et al (2005) Donor fibroblast chimerism in the pathogenic fibrotic lesion of human chronic graft-versus-host disease. Invest Ophthalmol Vis Sci 46:4519–4527
22. Na KS, Yoo YS, Hwang KY, Mok JW, Joo CK (2015) Tear osmolarity and ocular surface parameters as diagnostic markers of ocular graft-*versus*-host disease. Am J Ophthalmol 160:143–149
23. Pathak M, Diep PP, Lai X, Brinch L, Ruud E, Drolsum L (2018) Ocular findings and ocular graft-versus-host disease after allogeneic stem cell transplantation without total body irradiation. Bone Marrow Transplant 53:863–872
24. Nichols KK, Mitchell GL, Zadnik K (2004) The repeatability of clinical measurements of dry eye. Cornea 23:272–285
25. Ban Y, Ogawa Y, Ibrahim OM et al (2011) Morphologic evaluation of meibomian glands in chronic graft-versus-host disease using in vivo laser confocal microscopy. Mol Vis 17:2533–2543
26. Arita R, Itoh K, Inoue K et al (2008) Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology 115:911–915
27. Giannaccare G, Vigo L, Pellegrini M et al (2018) Ocular surface workup with automated noninvasive measurements for the diagnosis of meibomian gland dysfunction. Cornea 37:740–745
28. Engel LA, Wittig S, Bock F et al (2015) Meibography and meibomian gland measurements in ocular graft-versus-host disease. Bone Marrow Transpl 50:961–967
29. Kusne Y, Temkit M, Khera N et al (2017) Conjunctival subepithelial fibrosis and meibomian gland atrophy in ocular graft-versus-host disease. Ocul Surf 15:784–788
30. Que L, Zhang X, Li M (2017) Single-center retrospective study on meibomian gland loss in patients with ocular chronic graft-versus-host disease. Eye Contact Lens 0:1–7
31. Giannaccare G, Bonifazi F, Sessa M et al (2016) Dry eye disease is already present in hematological patients before hematopoietic stem cell transplantation. Cornea 35:638–643
32. Giannaccare G, Bonifazi F, Sessa M et al (2017) Ocular surface analysis in hematological patients before and after allogeneic hematopoietic stem cell transplantation: implication for daily clinical practice. Eye (Lond) 31:1417–1426
33. Giannaccare G, Bonifazi F, Sebastiani S et al (2018) Meibomian gland dropout in hematological patients before hematopoietic stem cell transplantation. Cornea 37:1264–1269
34. Mohammadpour M (2007) Progressive corneal vascularization caused by graft-versus-host disease. Cornea 26:225–226
35. Tranos PG, Forbes J, Jagger J (2001) Corneal perforation in chronic graft-versus-host disease. Eye (Lond) 15:111–113
36. Mohammadpour M, Maleki S, Hashemi H et al (2016) Recurrent corneal perforation due to chronic graft versus host disease; a clinicopathologic report. J Ophthalmic Vis Res 11:108–111
37. Kheirkhah A, Rahimi Darabad R, Cruzat A et al (2015) Corneal epithelial immune dendritic cell alterations in subtypes of dry eye disease: a pilot in vivo confocal microscopic study. Invest Ophthalmol Vis Sci 56:7179–7185
38. Kheirkhah A, Qazi Y, Arnoldner MA, Suri K, Dana R (2016) In vivo confocal microscopy in dry eye disease associated with chronic graft-versus-host disease. Invest Ophthalmol Vis Sci 57: 4686–4691
39. Tepelus TC, Chiu GB, Maram J et al (2017) Corneal features in ocular graft-versus-host disease by in vivo confocal microscopy. Graefes Arch Clin Exp Ophthalmol 255:2389–2397
40. He J, Ogawa Y, Mukai S et al (2017) In vivo confocal microscopy evaluation of ocular surface with graft-versus-host disease-related dry eye disease. Sci Rep 7:10720
41. Giannaccare G, Pellegrini M, Sebastiani S, Moscardelli F, Versura P, Campos EC (2019) In vivo confocal microscopy morphometric analysis of corneal subbasal nerve plexus in dry eye disease using newly developed fully automated system. Graefes Arch Clin Exp Ophthalmol. https://doi.org/10.1007/s00417-018-04225-7

42. Robinson MR, Lee SS, Rubin BI et al (2004) Topical corticosteroid therapy for cicatricial conjunctivitis associated with chronic graft-versus-host disease. Bone Marrow Transplant 33:1031–1035
43. Tabbara KF, Al-Ghamdi A, Al-Mohareb F et al (2009) Ocular findings after allogeneic hematopoietic stem cell transplantation. Ophthalmology 116:1624–1629
44. Hosseini H, Kumar PV, Geramizadeh B et al (2010) Conjunctival scrape cytology findings in patients with chronic graft-versus-host disease following allogeneic bone marrow transplantation. Acta Cytol 54:272–276
45. Sivaraman KR, Jivrajka RV, Soin K et al (2016) Superior limbic keratoconjunctivitis-like inflammation in patients with chronic graft-versus-host disease. Ocul Surf 14:393–400
46. Cher I (2000) Superior limbic keratoconjunctivitis: multifactorial mechanical pathogenesis. Clin Exp Ophthalmol 28:181–184
47. Di Pascuale MA, Espana EM, Liu DT et al (2005) Correlation of corneal complications with eyelid cicatricial pathologies in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. Ophthalmology 112:904–912
48. Knop N, Korb DR, Blackie CA, Knop E (2012) The lid wiper contains goblet cells and goblet cell crypts for ocular surface lubrication during the blink. Cornea 31:668–679
49. Nassiri N, Eslani M, Panahi N, Mehravaran S, Ziaei A, Djalilian AR (2013) Ocular graft versus host disease following allogeneic stem cell transplantation: a review of current knowledge and recommendations. J Ophthalmic Vis Res 8:351–358
50. Jabs DA, Wingard J, Green WR et al (1989) The eye in bone marrow transplantation. III. Conjunctival graft-vs-host disease. Arch Ophthalmol 107:1343–1348
51. Jack MK, Jack GM, Sale GE et al (1983) Ocular manifestations of graft-v-host disease. Arch Ophthalmol 101:1080–1084
52. Arocker-Mettinger E, Skorpik F, Grabner G et al (1991) Manifestations of graft-versus-host disease following allogenic bone marrow transplantation. Eur J Ophthalmol 1:28–32
53. Shikari H, Antin JH, Dana R (2013) Ocular graft-versus-host disease: a review. Surv Ophthalmol 58:233–251
54. Sullivan KM (1999) Graft-versus-host-disease. In: Forman SJ (ed) Hematopoietic cell transplantation. Blackwell, Oxford, pp 515–536
55. Jabs DA (1996) Ocular complications of bone marrow transplantation. In: Pepose J, Wilhelmus K (eds) Ocular infection and immunity. Mosby, St. Louis, pp 426–434
56. Kim SK (2004) Ocular graft versus host disease. In: Krachmer JH, Mannis MJ, Holland EJ (eds) Cornea. Mosby, St Louis, pp 879–885
57. Giannaccare G, Bernabei F, Pellegrini M et al (2019) Eyelid metrics assessment in patients with chronic ocular graft versus-host disease. Ocul Surf 17:98–103
58. Arafat SN, Robert MC, Abud T et al (2017) Elevated neutrophil elastase in tears of ocular graft-versus-host disease patients. Am J Ophthalmol 176:46–52
59. Nair S, Vanathi M, Mahapatra M et al (2018) Tear inflammatory mediators and protein in eyes of post allogenic hematopoeitic stem cell transplant patients. Ocul Surf 16:352–367
60. Satchi K, McNab AA (2016) Conjunctival cicatrizing disease presenting with lacrimal obstruction. Orbit 35:321–323
61. Campbell AA, Jakobiec FA, Rashid A et al (2016) Bilateral sequential dacryocystitis in a patient with graft-versus-host disease. Ophthal Plast Reconstr Surg 32:89–92
62. Hanada R, Ueoka Y (1989) Obstruction of nasolacrimal ducts closely related to graft-versus-host disease after bone marrow transplantation. Bone Marrow Transplant 4:125–126
63. Cahill KV, Burns JA (1993) Management of acute dacryocystitis in adults. Ophthal Plast Reconstr Surg 9:38–41
64. von Thun Und Hohenstein-Blaul N, Funke S, Grus FH (2013) Tears as a source of biomarkers for ocular and systemic diseases. Exp Eye Res 117:126–137
65. Riemens A, Stoyanova E, Rothova A, Kuiper J (2012) Cytokines in tear fluid of patients with ocular graft-versus-host disease after allogeneic stem cell transplantation. Mol Vis 18:797–802
66. Jung JW, Han SJ, Song MK et al (2015) Tear cytokines as biomarkers for chronic graft-versus-host disease. Biol Blood Marrow Transplant 21:2079–2085
67. Cocho L, Fernandez I, Calonge M et al (2016) Biomarkers in ocular chronic graft versus host disease: tear cytokine- and chemokine-based predictive model. Invest Ophthalmol Vis Sci 57:746–758
68. Gerber-Hollbach N, Plattner K, O'Leary OE et al (2018) Tear film proteomics reveal important differences between patients with and without ocular GvHD after allogeneic hematopoietic cell transplantation. Invest Ophthalmol Vis Sci 59:3521–3530
69. Wolffsohn JS, Arita R, Chalmers R et al (2017) TFOS DEWS II diagnostic methodology report. Ocul Surf 15:539–574
70. Berchicci L, Iuliano L, Miserocchi E et al (2014) Tear osmolarity in ocular graft-versus-host disease. Cornea 33:1252–1256
71. Schargus M, Meyer-ter-Vehn T, Menrath J, Grigoleit GU, Geerling G (2015) Correlation between tear film osmolarity and the disease score of the International Chronic Ocular Graft-Versus-Host-Disease Consensus Group in hematopoietic stem cell transplantation patients. Cornea 34:911–916
72. Carpenter PA, Kitko CL, Elad S et al (2015) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group report. Biol Blood Marrow Transplant 21:1167–1187
73. Lin X, Cavanagh HD (2015) Ocular manifestations of graft-versus-host disease: 10 years' experience. Clin Ophthalmol 9:1209–1213
74. Doughty MJ, Glavin S (2009) Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. Ophthalmic Physiol Opt 29:573–583
75. Bernauer W, Thiel MA, Langenauer UM et al (2006) Phosphate concentration in artificial tears. Graefes Arch Clin Exp Ophthalmol 244:1010–1014
76. Sabti S, Halter JP, Braun Fränkl BC et al (2012) Punctal occlusion is safe and efficient for the treatment of keratoconjunctivitis sicca in patients with ocular GvHD. Bone Marrow Transplant 47:981–984
77. Yin Y, Gong L (2017) Reversibility of gland dropout and significance of eyelid hygiene treatment in meibomian gland dysfunction. Cornea 36:332–337
78. Geerling G, Tauber G, Baudouin C et al (2011) The International Workshop on Meibomian Gland Dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci 52:2050–2064
79. Giannaccare G, Pellegrini M, Sebastiani S et al (2019) Efficacy of omega-3 fatty acid supplementation for the treatment of dry eye disease: a meta-analysis of randomized controlled trials. Cornea. https://doi.org/10.1097/ICO.0000000000001884
80. Yin J, Kheirkhah A, Dhlman T, Saboo U, Dana R (2018) Reduced efficacy of low-dose topical steroids in dry eye disease associated with graft-versus-host disease. Am J Ophthalmol 190:17–23
81. Inamoto Y, Petricek I, Burns L et al (2018) 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. https://doi.org/10.1038/s41409-018-0339-6

82. Rao SN, Rao RD (2006) Efficacy of topical cyclosporine 0.05% in the treatment of dry eye associated with graft versus host disease. Cornea 25:674–678
83. Lelli GJ Jr, Musch DC, Gupta A et al (2006) Ophthalmic cyclosporine use in ocular GVHD. Cornea 25:635–638
84. Wang Y, Ogawa Y, Dogru M et al (2008) Ocular surface and tear functions after topical cyclosporine treatment in dry eye patients with chronic graft-versus-host disease. Bone Marrow Transplant 41:293–302
85. Malta JB, Soong HK, Shtein RM et al (2010) Treatment of ocular graft-versus-host disease with topical cyclosporine 0.05%. Cornea 29:1392–1396
86. Boynton GE, Raoof D, Niziol LM, Hussain M, Mian SI (2015) 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 34:725–732
87. Abud TB, Amparo F, Saboo US, Di Zazzo A, Dohlman TH, Ciolino JB, Hamrah P, Dana R (2016) A clinical trial comparing the safety and efficacy of topical tacrolimus versus methylprednisolone in ocular graft-versus-host disease. Ophthalmology 123: 1449–1457
88. Takahide K, Parker PM, Wu M et al (2007) Use of fluid-ventilated, gas-permeable scleral lens for management of severe keratoconjunctivitis sicca secondary to chronic graft-versus-host disease. Biol Blood Marrow Transplant 13:1016–1021
89. Jacobs DS, Rosenthal P (2007) Boston scleral lens prosthetic device for treatment of severe dry eye in chronic graft-versus-host disease. Cornea 26:1195–1199
90. Schornack MM, Baratz KH, Patel SV et al (2008) Jupiter scleral lenses in the management of chronic graft versus host disease. Eye Contact Lens 34:302–305
91. Theophanous C, Irvine JA, Parker P, Chiu GB (2015) Use of prosthetic replacement of the ocular surface ecosystem scleral lenses in patients with ocular chronic graft-versus-host disease. Biol Blood Marrow Transplant 21:2180–2184
92. Giannaccare G, Versura P, Buzzi M, Primavera L, Pellegrini M, Campos EC (2017) Blood derived eye drops for the treatment of cornea and ocular surface diseases. Transfus Apher Sci 56:595–604
93. Ogawa Y, Okamoto S, Mori T et al (2003) Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. Bone Marrow Transplant 31:579–583
94. Tahmaz V, Gehlsen U, Sauerbier L et al (2017) 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 101:322–326
95. Stenwall PA, Bergstrom M, Seiron P et al (2015) Improving the anti-inflammatory effect of serum eye drops using allogeneic serum permissive for regulatory T cell induction. Acta Ophthalmol 93:654–657
96. Chiang CC, Lin JM, Chen WL, Tsai YY (2007) Allogeneic serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. Cornea 26:861–863
97. Na KS, Kim MS (2012) Allogeneic serum eye drops for the treatment of dry eye patients with chronic graft-versus-host disease. J Ocul Pharmacol Ther 28:479–483
98. Buzzi M, Versura P, Grigolo B et al (2018) Comparison of growth factor and interleukin content of adult peripheral blood and cord blood serum eye drops for cornea and ocular surface diseases. Transfus Apher Sci 57:549–555
99. Yoon KC, Jeong IY, Im SK, Park YG, Kim HJ, Choi J (2007) Therapeutic effect of umbilical cord serum eyedrops for the treatment of dry eye associated with graft-versus-host disease. Bone Marrow Transplant 39:231–235
100. Peric Z, Skegro I, Durakovic N et al (2018) Amniotic membrane transplantation-a new approach to crossing the HLA barriers in the treatment of refractory ocular graft-versus-host disease. Bone Marrow Transplant 53:1466–1469
101. Di Zazzo A, Kheirkhah A, Abud TB, Goyal S, Dana R (2017) Management of high-risk corneal transplantation. Surv Ophthalmol 62:816–827
102. Pellegrini G, Traverso CE, Franzi AT et al (1999) Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. Lancet 349:990–993
103. Holland EJ, Mogilishetty G, Skeens HM et al (2012) Systemic immunosuppression in ocular surface stem cell transplantation: results of a 10-year experience. Cornea 31:655–661
104. Meller D, Fuchsluger T, Pauklin M, Steuhl KP (2009) Ocular surface reconstruction in graft-versus-host disease with HLA-identical living-related allogeneic cultivated limbal epithelium after hematopoietic stem cell transplantation from the same donor. Cornea 28:233–236
105. Starzl TE, Demetris AJ (1998) Transplantation tolerance, microchimerism, and the two-way paradigm. Theor Med Bioeth 19:441–455
106. Busin M, Giannaccare G, Sapigni L et al (2017) Conjunctival and limbal transplantation from the same living-related bone marrow donor to patients with severe ocular graft-vs-host disease. JAMA Ophthalmol 135:1123–1125
107. Biber JM, Skeens HM, Neff KD, Holland EJ (2011) The Cincinnati procedure: technique and outcomes of combined living-related conjunctival limbal allografts and keratolimbal allografts in severe ocular surface failure. Cornea 30:765–771
108. Donnenfeld E, Pflugfelder SC (2009) Topical ophthalmic cyclosporine: pharmacology and clinical uses. Surv Ophthalmol 54: 321–338
109. Sosne G, Ping Qiu P, Kurpakus-Wheater M (2007) Thymosin beta 4: a novel corneal wound healing and anti-inflammatory agent. Clin Ophthalmol 1:201–207
110. Han X, Liu Y, Kam WR, Sullivan DA (2018) Effect of brimonidine, an α2 adrenergic agonist, on human meibomian gland epithelial cells. Exp Eye Res 170:20–28