Biol Blood Marrow Transplant 25 (2019) e46–e54

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Review

# Ocular Graft-versus-Host Disease after Hematopoietic Cell Transplantation: Expert Review from the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and Transplant Complications Working Party of the European Society of Blood and Marrow Transplantation

Yoshihiro Inamoto[1,*,†], Nuria Valdés-Sanz[2,†], Yoko Ogawa[3], Monica Alves[4], Luigi Berchicci[5], John Galvin[6], Hildegard Greinix[7], Gregory A. Hale[8], Biljana Horn[9], Debra Kelly[9], Hien Liu[10], Scott Rowley[11], Helene Schoemans[12], Ami Shah[13], Maria Teresa Lupo Stanghellini[14], Vaibhav Agrawal[15], Ibrahim Ahmed[16], Asim Ali[17], Neel Bhatt[18], Michael Byrne[19], Saurabh Chhabra[18], Zachariah DeFilipp[20], Kristina Fahnehjelm[21], Nosha Farhadfar[9], Erich Horn[9], Catherine Lee[22], Sunita Nathan[23], Olaf Penack[24], Pinki Prasad[25], Seth Rotz[26], Alicia Rovó[27], Jean Yared[28], Steven Pavletic[29], Grzegorz W. Basak[30], Minoo Battiwalla[31], Rafael Duarte[32], Bipin N. Savani[19], Mary E.D. Flowers[33], Bronwen E. Shaw[18], Igor Petriček[34,†]

[1] *Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan*
[2] *Department of Ophthalmology, Puerta de Hierro University Hospital, Madrid, Spain*
[3] *Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan*
[4] *Department of Ophthalmology, University of Campinas, Campinas, Brazil*
[5] *Ophthalmology Department, San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy*
[6] *Department of Medicine, University of Illinois at Chicago, Chicago, Illinois*
[7] *Bone Marrow Transplantation Unit, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria*
[8] *Department of Hematology/Oncology, Johns Hopkins All Children's Hospital, St Petersburg, Florida*
[9] *UFHealth Shands Cancer Hospital, University of Florida, Gainesville, Florida*
[10] *H. Lee Moffitt Cancer Center, Cleveland, Ohio*
[11] *Hackensack University Medical Center, Washington, DC*
[12] *Department of Hematology, University Hospital Leuven, Leuven, Belgium*
[13] *Division of Stem Cell Transplantation and Regenerative Medicine, Lucille Packard Children's Hospital, Stanford School of Medicine, Palo Alto, California*
[14] *Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Scientific Institute, Milano, Italy*
[15] *Simon Cancer Center, Indiana University, Indianapolis, Indiana*
[16] *Department of Hematology Oncology and Bone Marrow Transplantation, The Children's Mercy Hospitals and Clinics, Kansas City, Missouri*
[17] *Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*
[18] *Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[19] *Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee*
[20] *Blood and Marrow Transplant Program, Massachusetts General Hospital, Boston, Massachusetts*
[21] *Department of Clinical Neuroscience, Karolinska Institute, St Erik Eye Hospital, Stockholm, Sweden*
[22] *Utah Blood and Marrow Transplant Program, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah*
[23] *Rush University Medical Center, Chicago, Illinois*
[24] *Division of Hematology and Oncology, Department of Internal Medicine, Charité University Medicine, Campus Rudolf Virchow, Berlin, Germany*
[25] *Lousiana State University Children's Hospital, New Orleans, Louisiana*
[26] *Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*
[27] *Bern University Hospital, Bern, Switzerland*
[28] *Blood and Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Cancer Center, University of Maryland, Baltimore, Maryland*
[29] *Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*
[30] *Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland*
[31] *Hematology Branch, Sarah Cannon BMT Program, Nashville, Tennessee*
[32] *Hematopoietic Transplantation and Hemato-oncology Section, Puerta de HierroUniversity Hospital, Madrid, Spain*
[33] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[34] *Department of Ophthalmology, University Clinical Hospital Zagreb, Zagreb, Croatia*

*Financial disclosure*: See Acknowledgments on page e51.

* Correspondence and reprint requests: Yoshihiro Inamoto, MD, PhD, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo, Tokyo 104-0045, Japan.
*E-mail address:* yinamoto@ncc.go.jp (Y. Inamoto).

https://doi.org/10.1016/j.bbmt.2018.11.021

*Article history:*
Received 23 August 2018
Accepted 15 November 2018

*Key Words:*
Chronic graft-versus-host disease
Eye
Review
Biology
Treatment
Hematopoietic cell transplantation

A B S T R A C T
Ocular graft-versus-host disease (GVHD) occurs in more than one-half of patients who develop chronic GVHD after allogeneic hematopoietic cell transplantation (HCT), causing prolonged morbidity that affects activities of daily living and quality of life. Here we provide an expert review of ocular GVHD in a collaboration between transplantation physicians and ophthalmologists through the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and the Transplant Complications Working Party of the European Society of Blood and Marrow Transplantation. Recent updates in ocular GVHD regarding pathophysiology, preclinical models, risk factors, prevention, screening, diagnosis, response criteria, evaluation measures, and treatment are discussed. Ocular GVHD involves at least 3 biological processes: lacrimal gland dysfunction, meibomian gland dysfunction, and corneoconjunctival inflammation. Preclinical models have identified several novel pathogenic mechanisms, including the renin angiotensin system and endoplasmic reticulum stress signaling, which can be targeted by therapeutic agents. Numerous studies have identified reliable tests for establishing diagnosis and response assessment of ocular GVHD. The efficacy of systemic and topical treatment for ocular GVHD is summarized. It is important that all health professionals caring for HCT recipients have adequate knowledge of ocular GVHD to provide optimal care.


## INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment for many hematologic malignancies and nonmalignant disorders. Chronic graft-versus-host disease (GVHD) is a leading cause of late morbidity and mortality in HCT survivors, compromising both quality of life (QOL) and function [1]. Ocular involvement is common in patients with chronic GVHD, with an incidence of >50% [2–5]. Because the ocular surface can be evaluated by physicians and ophthalmologists, it is important for all health professionals caring for HCT recipients to have adequate knowledge of ocular GVHD.

This expert review summarizes recent updates in ocular GVHD regarding pathophysiology, preclinical models, risk factors, prevention, screening, diagnosis, response criteria, evaluation measures, and treatment. It characterizes the state of the science of ocular GVHD after HCT in a collaboration between transplantation physicians and ophthalmologists through the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the Transplant Complications Working Party of the European Society of Blood and Marrow Transplantation (EBMT). We provide evidence-based recommendations for clinical practice and future areas of research.

### METHODS

We searched the MEDLINE/PubMed database using a broad search strategy to identify studies related to ocular complications after HCT. The primary search was conducted using the terms "hematopoietic transplantation AND (eye OR ocular)," and 552 articles were identified as of March 31, 2018. Relevant articles were also reviewed as needed. Recommendations are organized according to an evidence-based system as described previously [6] to reflect the strength of recommendations and the quality of evidence supporting the recommendations (Table 1).

## SYMPTOMS AND SIGNS

Manifestations of ocular GVHD range from mild conjunctivitis to severe cicatricial conjunctivitis and corneal perforation [7]. The most commonly reported symptom of ocular GVHD is keratoconjunctivitis sicca (KCS), commonly known as dry eye [7,8] which typically develops by 6 to 9 months after allogeneic HCT [3,9]. Symptoms of ocular GVHD include irritation, burning, pain, redness, photophobia, blurry vision, excessive tearing, and a sensation of sand or grit in the eyes [9,10]. Along with dry eye, conjunctival injection is another important sign of ocular GVHD that can be easily recognized by any health professional.

## PATHOPHYSIOLOGY

The tear film is composed of 3 layers: aqueous, lipid, and mucin. Subtypes of dry eye include the evaporative type and the deficiency type of aqueous or mucin tear film [11]. The evaporative type is due to deficiency of the lipid layer, causing rapid evaporation of the aqueous layer. The aqueous or mucin deficiency of the tear occurs when the lacrimal gland is affected by any kind of damage. All abnormalities are seen in patients with ocular GVHD [3,11].

Ocular GVHD involves at least 3 important biological processes: lacrimal gland dysfunction, meibomian gland dysfunction, and corneoconjunctival inflammation. As with chronic GVHD at other sites, the initial phase of ocular GVHD is thought to be a T cell- mediated inflammatory process, and the subsequent phase is a result of an immune cascade leading to fibrotic changes in glands and ineffective tear film that cause ocular surface damage [3,12]. The medium-sized ducts in lacrimal gland are preferentially targeted by T cells and other inflammatory cells in the initial phase, and the ducts of lacrimal and meibomian glands and nasolacrimal ducts are frequently obstructed by immune-mediated fibrosis [13,14]. Other potentially affected areas include the cornea, limbus, and conjunctiva [11].

The main histologic findings in the affected ocular surface are marked fibrosis of the subepithelial interstitium [15,16], prominent increase in the number of $CD34^+$ fibroblasts in the lacrimal glands, and lymphocytic infiltration of the lacrimal glands [14]. T cells are detected mainly in the periductal area, with some T cells infiltrating into ductal epithelia through disrupted laminae in lacrimal glands. T cells infiltrating ductal epithelia are primarily activated $CD8^+$ cytotoxic T cells, indicating that T cell invasion leads to the destruction of ductal epithelium of lacrimal glands. Based on these findings, chronic GVHD in the lacrimal gland is explained by a T cell alloimmune response to ductal epithelium [13,17].

Tear film osmolality and the level of cytokines, including IL-6, IL-8, IL-17, IFN-$\gamma$, TNF-$\alpha$, and chemokines such as CXCL8 and CXCL10 in tear fluid are elevated in ocular GVHD because of reduced tear production, increased

† Equal contribution.

**Table 1**
Evidence-Based Rating System Used in This Review

| Category | Definition |
|---|---|
| Strength of the recommendation | |
| A | Should always be offered. |
| B | Should generally be offered. |
| C | Evidence for efficacy is insufficient to support a recommendation for or against, or evidence for efficacy might not outweigh adverse consequences, or cost of the approach. Optional. |
| D | Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. |
| E | Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered. |
| Quality of evidence supporting the recommendation | |
| I | Evidence from at least 1 properly randomized, controlled trial. |
| II | Evidence for at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center) or from multiple time series or dramatic results from uncontrolled experiments. |
| III | Evidence from opinions of respected authorities based on clinical experience, descriptive. |

evaporation, and inflammation [18-21]. Extracellular DNA is also increased in tear fluid of patients with ocular GVHD and the use of DNase I eye drops may improve ocular surface inflammation [22]. In vivo confocal microscopy in patients with ocular GVHD has shown increased infiltration with globular immune cells and dendritic cells around the sub-basal nerve of the central cornea and limbal region [23], demonstrating that immunocompetent cells infiltrate into avascular corneal lesions in ocular GVHD.

## PRECLINICAL MODELS

Several murine models of ocular GVHD have been studied previously [17,24,25]. In vitro analysis has shown that fibroblasts derived from GVHD-involved lacrimal glands have highly proliferative, invasive, and migratory characteristics [26]. Murine models have shown that interaction between T cells and antigen-presenting cells, including macrophages contributed to the pathogenesis of ocular GVHD [17]. Migrating donor mesenchymal stem cells interact with T cells, leading to production of IL-6, a reduction of regulatory T cells, and an increase in Th17 effector T cells similar to what is seen in autoimmune pathologic processes [25].

Several novel therapeutic targets are emerging from murine models of ocular GVHD. The tissue renin-angiotensin system in the lacrimal gland is implicated with pathologic fibrosis in GVHD. Angiotensin II type 1 receptor antagonist ameliorates fibrosis of the lacrimal gland in murine models [27]. Endoplasmic reticulum (ER) stress signaling is elevated in lacrimal glands affected by GVHD. The suppression of ER stress by 4-phenylbutyric acid improved ocular GVHD and survival in a murine model [28]. Heavy-chain hyaluronan pentraxin 3, a complex purified from human amniotic membrane, is known to exert anti-inflammatory and antiscarring actions, as well as reduced gene expression of collagen type I, collagen type III, and nuclear factor kappa-light-chain-enhancer of activated B cells in murine lacrimal glands affected by GVHD [29].

## INCIDENCE

The incidence of ocular GVHD varies widely in published studies, owing in part to differences in the diagnostic criteria used. In a single-center study of 172 patients [10], ocular GVHD was defined as a new onset of at least 2 of 5 parameters: new-onset dry eye symptoms, tear breakup time $\leq$5 seconds, Schirmer test $\leq$5 mm at 5 minutes, vital staining grade I or higher, and conjunctival inflammation. Using this definition, ocular GVHD was present in 16% of patients by 100 days after allogeneic HCT, and the cumulative incidence increased to 35% at 2 years after HCT [10]. A similar incidence of 33% was reported in a study of 635 patients using the 2005 National Institutes of Health (NIH) diagnostic criteria that include the Schirmer test [30]. In a prospective multicenter study of patients with chronic GVHD (diagnosed according to the 2005 NIH criteria), the eyes were the third most commonly involved organ, affecting 51% of patients at the time of chronic GVHD diagnosis. In another study, the majority of patients with eye involvement had a moderate (65%) or severe (32%) eye score by the NIH criteria [31].

## RISK FACTORS

Risk factors associated with the onset of ocular GVHD are summarized in Table 2. Several studies have identified previous acute GVHD [10,30], use of peripheral blood stem cells [30,32], and HCT from a female donor to a male recipient [10,33] as associated with ocular GVHD. A single retrospective study identified the absence of antithymocyte globulin prophylaxis, more organs with GVHD, non-Caucasian patient, and Epstein-Barr virus-seropositive donor as associated with ocular GVHD [30,34].

## EVALUATION MEASURES

Evaluation of ocular GVHD includes measures that can be used by hematologists in the clinic, as well as more specialized measures used by ophthalmologists. Recommended levels for diagnostic and response measures are summarized separately in Table 3.

### *Schirmer Test: Tear Volume Assessment*

The Schirmer test without anesthesia is a standard assessment method that can be performed by hematologists in some centers. It is performed by placing the folded Schirmer paper strip over the temporal one-third of the lower lid margin to measure the extent of wetting after a 5-minute period. Administering the test with the patient's eyes closed may minimize the variability of the results. Diagnostic cutoff values of 5 to 10 mm in 5 minutes have been proposed, and the Schirmer test has shown >80% diagnostic sensitivity and specificity for ocular GVHD [20,35–37]. However, the Schirmer test is inaccurate, variable, and not inclusive of the evaporative aspect of dry eye and has poor correlation with other tests and treatment responses [38,39].

### *Ocular Surface Disease Index: Ocular Symptom Assessment*

Several questionnaires have been used in clinical trials to document dry-eye related symptoms, including the Ocular Surface Disease Index (OSDI) [40], Standard Patient Evaluation

**Table 2**
Risk Factors Associated with the Onset of Ocular GVHD

| Risk factor |
|---|
| Previous acute GVHD [10,30] |
| Use of peripheral blood stem cells [30,32] |
| Transplantation from a female donor to a male recipient [10,33] |
| Absence of antithymocyte globulin prophylaxis [30] |
| Larger number of organs involved with GVHD [30] |
| Non-Caucasian [34] |
| Epstein-Barr virus-seropositive donor [34] |

**Table 3**
Evaluation Measures for Ocular GVHD

| Measure | Recommendation Level | |
|---|---|---|
| | Diagnosis | Response Measure |
| Hematologist assessment | | |
| NIH eye score | A-II [37] | A-II [39] |
| Schirmer test without anesthesia | A-II [20,34–36] | D-II [38,39] |
| OSDI | B-II [35] | B-II [39] |
| Lee eye subscale | B-II [37] | B-II [37,39] |
| Patient-reported global rating of eye symptoms (0-10) | B-II [37] | B-II [39] |
| Ophthalmologist assessment | | |
| Corneal staining | A-II [35,37] | B-II* [37] |
| TBUT | B-II [35,37] | B-III |
| ICOGCG score | B-II [35,54] | C-III |
| Meibomian score† | B-II [37] | C-III |
| LIPCOF | C-II [47] | C-III |

*Oxford grand total score.
†Meibomian gland plugging: 0 = none; 1 = 1-2 glands; 2 = 2-3 glands; 3 = all 5 glands, lid margin swelling [37].

of Eye [41], and Dry Eye-Related Quality of Life Score [42]. Among these, the OSDI is most commonly used worldwide. The OSDI consists of 12 patient-reported questions related to dry eye and is a valid and reliable instrument for measuring dry eye disease [40]. One study has shown 44% sensitivity and 98% specificity for the OSDI in the diagnosis of ocular GVHD [35]. The OSDI's utility as a response measure has been demonstrated in a prospective multicenter study [39].

### *Corneal Staining: Corneal Surface Integrity Assessment*

Fluorescein, a vital dye for staining the ocular surface, is extensively used in the diagnosis and management of dry eye disease. It can be used to stain damaged epithelium of both the cornea and the conjunctiva. Fluorescein is commonly used to evaluate the degree of corneal epitheliopathy. Lissamine green and rose bengal stains are also used for some grading criteria of dry eye disease. Instilled dye staining indicates ocular surface disease, with greater staining indicating greater severity of dry eye disease [36]. Among the several available methods for evaluating and grading staining include the 1995 National Eye Institute/Industry Workshop system, the area-density combination index, the Oxford Staining Score, and the Ocular Staining Score of the Sjögren International Collaborative Clinical Alliance [36]. Disruption in superficial cell tight junctions or defective glycocalyx causes damage to epithelial cells and staining by fluorescein dye. In one study, the sensitivity and specificity of corneal staining for the diagnosis of ocular GVHD were 91% and 54%, respectively [35].

### *Tear Film Breakup Time: Tear Film Stability Assessment*

The tear film breakup time (TBUT) is a standard measure for diagnosing dry eye and assessing treatment response [43]. The TBUT is the interval between a complete blink and the appearance of the first break in the tear film. The test is performed after instillation of sodium fluorescein to enhance visibility of the tear film. The patient is instructed to blink naturally 3 times and then stop blinking. The cutoff time for dry eye diagnosis ranges from $<$10 seconds to $<$5 seconds. It is important to use a controlled volume of fluorescein, such as 2 $\mu$L, for standardized measurement [3]. One study reported a sensitivity and specificity of TBUT for diagnosis of ocular GVHD of 80% and 67%, respectively [35].

### *Meibomian Score*

Several grading scales for meibomian gland dysfunction have been proposed and adopted in clinical practice [44]. These scales are based on findings for the lid margin or meibomian glands, although their utility for ocular GVHD has not been well validated. One study showed the utility of the meibomian gland plugging score (0 = none; 1 = 1 to 2 glands; 2 = 2 to 3 glands; 3 = all 5 glands, lid margin swelling) for diagnosing ocular GVHD [37].

### *Lid-Parallel Conjunctival Folds*

Conjunctivochalasis, or lid-parallel conjunctival folds (LIPCOF), are bulbar conjunctival folds that sit on top of the lower eyelid margin and can be observed using a slit lamp. Grading the extent of conjunctival folds as a sign of dry eye has been proposed by several investigators [45,46]. The most widely used grading system is the Höh scheme, a simple, noninvasive diagnostic test for dry eye diseases [46]. LIPCOF is measured above the temporal part of the lower eyelid and graded from 0 (no folds) to 3 (pronounced folds). Caveats for its usefulness are its subjectivity and inability to distinguish between hyposecretive and hyperevaporative dry eye. In a multicenter study, LIPCOF testing had moderate sensitivity and specificity and demonstrated a high positive predictive value as a simple, quick, and noninvasive dry eye screening tool [47].

## SCREENING AND PREVENTION

Comprehensive eye examination is recommended before HCT in all patients to assess the baseline condition [48]. A prospective study showed that reflex tearing was good in 86% of patients before HCT but began to decrease by around 3 months after HCT, and that the mean Schirmer test value decreased to $\leq$10 mm by around 6 months [3]. Thus, screening evaluation should start no later than 6 months after HCT in all patients [49]. Systematic GVHD screening is essential for early recognition of ocular GVHD. Some experts recommend routine ophthalmologic screening evaluation at 3 months and 12 months after HCT, as well as at the time of initial diagnosis of chronic GVHD of any site [50].

No specific prevention strategies have been established except for prevention of chronic GVHD by T cell depletion with therapies such as antithymocyte globulin, post-transplantation cyclophosphamide and CD34 selection [51,52]. The efficacy of cyclosporine eye drops for prevention of ocular GVHD is currently under investigation in a randomized Phase III study (ClinicalTrials.gov identifier NCT00755040).

## DIAGNOSIS, STAGING, AND RESPONSE CRITERIA

The 2014 NIH criteria define a simple symptom-based diagnosis of ocular GVHD [7], in which ocular GVHD is the new onset of dry, gritty, or painful eyes with decreased values in the Schirmer test without anesthesia in a patient after allogeneic HCT. The severity of ocular GVHD is defined as a score of 0 to 3, based on the type of supportive care required and the effect of the symptoms on activities of daily living (ADL). A score of 1 is assigned for the use of lubricant eye drops $<$3 times a day with no need for punctal plugs and no impact on ADL. A score of 3 is assigned for the inability to work, the loss of vision due to KCS, or the need for special eyewear [7]. All other moderately symptomatic situations are assigned a score of 2. The NIH eye score combined with the Schirmer test has shown $>$90% sensitivity and specificity for the diagnosis of ocular GVHD [37]. In the context of response assessment in clinical trials, the NIH eye score is recommended as a simple and reliable measure [48], whereas the Schirmer test is no

longer recommended because of its poor correlation with changes in ocular GVHD symptoms [39]. Other useful tools for response assessment include the Lee eye subscale, the 10-point patient-reported chief eye complaint, and the OSDI [39].

In 2013, the International Chronic Ocular GVHD Consensus Group (ICOGCG) proposed new diagnostic metrics to improve objectivity in the diagnosis and follow-up of chronic GVHD [53]. Measures are obtained by ophthalmologic examination using the Schirmer test without anesthesia, corneal staining and conjunctival injection, and patient-reported dry eye symptoms on the OSDI. The presence of systemic chronic GVHD is also taken into account, and a higher score is required for a diagnosis of probable ocular GVHD in patients without involvement of other organs [53]. A study comparing diagnostic utility between the 2005 NIH criteria and the ICOGCG criteria showed that the more stringent ICOGCG criteria better differentiated ocular GVHD [35]. Validation of ICOGCG diagnostic criteria, in comparison with diagnosis based on best clinical practice, showed good agreement and reproducibility, especially in more severe cases of ocular GVHD [54]. Further validation of the ICOGCG score, particularly for the applicability in clinical practice and as a response measure, is needed.

## TREATMENT

The goals of treatment for chronic GVHD are reduction of symptom burden, sustained control of disease activity, and prevention of tissue damage and disability without toxicity [50]. Ocular GVHD is often treated in a stepwise fashion, beginning with the simplest treatment and transitioning to increasingly aggressive intervention as needed. An ophthalmologist knowledgeable in ocular GVHD should be involved with patient care. Recommended treatments for ocular GVHD are summarized in Table 4. Mild ocular GVHD often can be treated with topical therapy [55,56].

**Table 4**
Recommendations for Evaluation and Treatment of Ocular GVHD

| Recommendation | Level |
|---|---|
| Evaluation by an ophthalmologist | |
| Before transplantation | A-III [48] |
| Between 3 and 6 mo after HCT in all patients | A-II [3,49] |
| At diagnosis of chronic GVHD in any site | A-III [50] |
| First-line systemic treatment for ocular GVHD* | |
| Corticosteroids | A-I [7,50,55] |
| Second- or subsequent-line systemic treatment for ocular GVHD* | |
| Extracorporeal photopheresis | C-II [58-61] |
| Rituximab | C-II [61,62] |
| Sirolimus | C-II [63,64] |
| Mycophenolate mofetil | C-II [66-68] |
| Topical treatment | |
| Preservation-free artificial tears or gels | A-II [8,56,69] |
| Viscous ointment/tears | A-II [8,56] |
| Cyclosporine | B-I [86,88,89] |
| Tacrolimus | B-I [91,92] |
| Punctal plugs | B-II [78,79] |
| Corticosteroids | B-II [8,90] |
| Warm compresses, lid hygiene | B-II [85] |
| Scleral lenses | B-II [80-83] |
| Tranilast | B-II [94] |
| Mucin secretagogues | B-II [42,70] |
| Occlusive eye wear | B-II [84] |
| Antibiotic eye drops or ointment | B-III [8] |
| Autologous serum eye drops | C-II [73-76] |
| Platelet derived eye drops | C-II [77] |
| Inhibitor of Janus and spleen tyrosine kinases | C-II [93] |
| Partial tarsorrhaphy | C-II [8] |
| Superficial epithelial debridement | C-III [8] |
| Amniotic membrane transplantation | C-III [97] |
| Limbal stem cell transplantation and keratoplasty | C-III [98,99] |
| Other treatment | |
| Low-dose oral tetracycline/doxycycline | B-II [87] |
| Oral omega-3 fatty acid supplement | C-I [71,72] |

* Systemic treatment for chronic GVHD is generally not used for isolated eye involvement or without topical treatment.

### *Indication for Systemic Treatment for Ocular GVHD*

In general, systemic immunosuppressive treatment is considered in patients with a moderate or severe NIH global score after taking overall condition, comorbidities, and risk of recurrent malignancy into account [7,55]. In a multicenter prospective observational study, the rate of complete or partial response of ocular GVHD as defined by the NIH criteria was 23% at 6 months after initial systemic treatment, which consisted mostly of corticosteroids and calcineurin inhibitors [57].

Data on the efficacy of individual systemic treatments specifically for ocular GVHD are limited, but response rates have been reported as a secondary endpoint in several prospective studies. The average response rates of ocular GVHD are 43% with extracorporeal photopheresis [58–61], 31% with rituximab [62,63], 60% with sirolimus [64,65], and 33% with mycophenolate mofetil [66–68] in a corticosteroid-refractory setting. These response rates should be interpreted with great caution owing to the small number of cases, variable response criteria, and differing timing of assessments in these studies.

### *Increase in Ocular Surface Moisture*

Intense lubrication is important for preserving the integrity of the ocular surface, diminishing lid-ocular surface friction and thus ocular discomfort, and diluting inflammatory mediators. Preservative-free artificial tears, viscous eye drops, and viscous ointment are recommended as lubricant therapy to decrease ocular complaints, prevent epithelial damage, and improve visual function [8,56]. Hyaluronic acid- and dexpanthenol-containing eye drops are recommended in patients with severe KCS [8,69]. Mucin secretagogue eye drops (eg, diquafosol, rebamipide) have shown effectiveness in patients with dry eye disease and ocular GVHD [42,70]. There are conflicting results of randomized studies with oral omega-3 fatty acids for improving tear film stability and dry eye symptoms [71,72].

Autologous serum eye drops are effective as lubricants and also have anti-inflammatory and nutritive effects on the ocular surface because they contain epitheliotrophic growth factors, cytokines, nerve growth factors, tissue inhibitors of matrix metalloproteinases, and complement factors [73-76]. Autologous serum eye drops must be prepared according to local regulations for blood products, are contraindicated for patients with active infections, and can be difficult to prepare in patients with anemia. In a prospective pilot study of 26 patients, platelet-derived eye drops improved ocular symptoms in 91% of patients and improved objective findings in 32% [77].

### *Control of Evaporation*

Punctal occlusion with collagen or silicone plugs is helpful to maintain lubrication of the ocular surface for patients with more than mild symptoms [8,53,78]. Permanent punctal occlusion by thermal cauterization or surgical occlusion can be performed in some patients [79]. Scleral contact lenses are effective in ameliorating symptoms in patients with severe ocular GVHD and can dramatically improve QOL in some patients [80-83]. Access to some scleral lenses is limited by their cost and regional availability [80,81], but bandage soft

contact lenses and other lenses are widely available and less-expensive options [82,83]. Moisture chamber goggles are effective as a supportive measure [84].

Treatment for blepharitis is also important for control of evaporation. Regular application of warm compresses and lid care with ointment or solution can improve meibomian gland dysfunction [85]. Topical antibiotic ointment or eye drops can be applied for bacterial superinfection of the lid margin [8]. Topical anti-inflammatory therapy with calcineurin inhibitors can reduce inflammation of the lids and lid margin in patients with blepharitis [86]. Low-dose oral tetracycline/doxycycline for at least 3 to 6 weeks can be effective in reducing inflammation, improving meibomian gland secretion and tear film lipid layer [8,87].

### *Decrease in Ocular Surface Inflammation*

Randomized studies have shown that the use of cyclosporine eye drops improves the Schirmer test results and tear film breakup time, increases the number of conjunctival goblet cells, and reduces punctate keratopathy in patients with KCS, including ocular GVHD [88,89]. Therefore, cyclosporine eye drops should be used for patients with inflammatory signs of ocular GVHD, as well as those without visible inflammation but with underlying inflammatory processes [8]. The recommended dose of cyclosporine eye drops in patients with chronic GVHD is .05% or .1% twice daily as long-term treatment [8].

Topical corticosteroids are able to promote lymphocyte apoptosis and suppress cell-mediated inflammation [90]. They are indicated in acute exacerbation of ocular GVHD and should be restricted to short-term treatment, and close monitoring by an ophthalmologist is recommended to monitor for adverse effects such as impaired epithelization, ocular hypertension, glaucoma, cataract formation, corneal thinning, and infectious keratitis [8]. Rimexolone and fluorometholone appear to be associated with a lower risk for the development of secondary glaucoma compared with prednisolone acetate [8].

A Phase I/II prospective, randomized, double-blind study showed that topical tacrolimus .05% was safe, well tolerated, and effective for ocular GVHD without the hypertensive effects of topical corticosteroids [91]. Topical .02% tacrolimus ointment also has exhibited rapid anti-inflammatory effects in patients with ocular GVHD, which allows a reduction of steroid use in the long term [92].

A topical inhibitor of Janus and spleen tyrosine kinases improved ocular GVHD in a pilot randomized study [93]. Topical tranilast improves symptoms of ocular GVHD through inhibition of transforming growth factor ß [94]. Topical anakinra 2.5%, an IL-1 receptor antagonist, improved symptoms and corneal epitheliopathy in patients with dry eye disease after 12 weeks of administration [95]. Topical lifitegrast, an integrin antagonist that inhibits LFA-1/ICAM-1 interaction, is a new Food and Drug Administration-approved treatment for dry eye disease [96]. In a randomized, placebo-controlled Phase I/II study (ClinicalTrials.gov identifier NCT02975557), brimonidine eye drops produced reductions in ocular redness and discomfort after 3 months of treatment. The efficacy of nanoemulsion eye drops of brimonidine is currently being tested in a Phase III study (ClinicalTrials.gov identifier NCT03591874). Topical treatment is usually continued for as long as symptoms are present and may be tapered and withdrawn after resolution of symptoms.

### *Surgical Intervention*

Superficial epithelial debridement is performed in filamentary keratopathy to promote epithelial healing [8]. Partial tarsorrhaphy may be important to decrease the exposed area of the corneal surface in severe dry eye [8]. Amniotic membrane transplantation has been performed in patients with refractory epithelial defects and corneal ulcerations to promote corneal healing and to prevent further corneal perforation [97]. Limbal epithelial transplantation and keratoplasty (ie, corneal transplantation) have been reported in patients with ocular GVHD but have been less beneficial in patients with ongoing inflammation [98,99]. Patients with epithelial defects need preservation-free antibiotic eye drops with low epithelial toxicity for prevention of infections.

## SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH

Ocular GVHD can cause prolonged morbidity affecting ADL and QOL. Timely diagnosis and early treatment of ocular GVHD are crucial to protect vision and prevent severe complications, such as corneal ulceration and perforation. Care of patients with ocular GVHD warrants close collaboration between transplantation physicians and ophthalmologists.

Future research should be directed toward establishing reliable and widely available tools for diagnosing and assessing response to treatment of ocular GVHD. Distinguishing active inflammation from its sequelae is important but is not addressed in current criteria. Several signs, such as pseudomembrane, limbal stem cell deficiency, corneal neovascularization, corneal conjunctivalization, nasolacrimal duct obstruction, severe conjunctival injection, corneal perforation, and LIPCOF may help distinguish active inflammation. In addition, there is controversy about acute GVHD of the eyes [16]. Eyes are not a target organ for acute GVHD according to the current consensus [7,100], and this is a topic for future studies.

As reviewed herein, preclinical models have also implicated inflammation, immune dysregulation, and fibrosis in ocular GVHD [15,17,23,24,26]. Novel agents that target specific pathways of chronic GVHD are currently under investigation, including Janus kinase inhibitors, Bruton's tyrosine kinase inhibitors, and Rho kinase inhibitors. Future studies should elucidate the efficacy of these agents in ocular GVHD. Emerging treatments for dry eye disease, such as anakinra and lifitegrast, should be tested in patients with ocular GVHD.

## ACKNOWLEDGMENTS

*Financial disclosure:* The CIBMTR is supported primarily by Public Health Service Grant/Cooperative Agreement 5U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases; Grant/Cooperative Agreement 4U10HL069294 from the NHLBI and NCI; Contract HHSH250201200016C with the Health Resources and Services Administration; Grants N00014-17-1-2388 and N0014-17-1-2850 from the Office of Naval Research; and grants from Actinium Pharmaceuticals*, Amgen*, Amneal Biosciences*, Angiocrine Bioscience*, anonymous donation to the Medical College of Wisconsin, Astellas Pharma US, Atara Biotherapeutics, Be the Match Foundation, bluebird bio*, Bristol Myers Squibb Oncology*, Celgene*, Cerus, Chimerix*, Fred Hutchinson Cancer Research Center, Gamida Cell, Gilead Sciences, HistoGenetics, Immucor, Incyte*, Janssen Scientific Affairs, Jazz Pharmaceuticals*, Juno Therapeutics, Karyopharm Therapeutics, Kite Pharma, Medac, MedImmune, The Medical College of Wisconsin, Mediware*, Merck & Co*, Mesoblast*;

MesoScale Diagnostics, Millennium, Takeda Oncology, Miltenyi Biotec*, National Marrow Donor Program, Neovii Biotech*, Novartis Pharmaceuticals, Otsuka Pharmaceutical, PCORI, Pfizer*, Pharmacyclics*, PIRCHE, Sanofi Genzyme*, Seattle Genetics*, Shire, Spectrum Pharmaceuticals, St Baldrick's Foundation, Sunesis Pharmaceuticals*, Swedish Orphan Biovitrum, Takeda Oncology, Telomere Diagnostics, and the University of Minnesota. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, Department of the Navy, Department of Defense, Health Resources and Services Administration, or any other agency of the US Government.

*Corporate members.

*Conflict of interest statement:* There are no conflicts of interest to report.

*Authorship statement:* Y.I., N.V.-S., and I.P. contributed equally to this work.

## REFERENCES

1. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2003;9:215–233.
2. Tichelli A, Duell T, Weiss M, et al. Late-onset keratoconjunctivitis sicca syndrome after bone marrow transplantation: incidence and risk factors. European Group for Blood and Marrow Transplantation (EBMT) Working Party on Late Effects. *Bone Marrow Transplant*. 1996;17:1105–1111.
3. Ogawa Y, Okamoto S, Wakui M, et al. Dry eye after haematopoietic stem cell transplantation. *Br J Ophthalmol*. 1999;83:1125–1130.
4. Flowers ME, Parker PM, Johnston LJ, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood*. 2002;100:415–419.
5. Westeneng AC, Hettinga Y, Lokhorst H, Verdonck L, van Dorp S, Rothova A. Ocular graft-versus-host disease after allogeneic stem cell transplantation. *Cornea*. 2010;29:758–763.
6. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes Of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant*. 2006;12:375–396.
7. Jagasia MH, Greinix HT, Arora M, 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.
8. Dietrich-Ntoukas T, Cursiefen C, Westekemper H, et al. 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*. 2012;31:299–310.
9. Shikari H, Amparo F, Saboo U, Dana R. Onset of ocular graft-versus-host disease symptoms after allogeneic hematopoietic stem cell transplantation. *Cornea*. 2015;34:243–247.
10. Jacobs R, Tran U, Chen H, et al. Prevalence and risk factors associated with development of ocular GVHD defined by NIH consensus criteria. *Bone Marrow Transplant*. 2012;47:1470–1473.
11. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf*. 2017;15:276–283.
12. Cooke KR, Luznik L, Sarantopoulos S, et al. The Biology of Chronic Graft-versus-Host Disease: a task force report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2017;23:211–234.
13. Ogawa Y, Kuwana M, Yamazaki K, 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;44:1888–1896.
14. Ogawa Y, Yamazaki K, Kuwana M, et al. A significant role of stromal fibroblasts in rapidly progressive dry eye in patients with chronic GVHD. *Invest Ophthalmol Vis Sci*. 2001;42:111–119.
15. Kusne Y, Temkit M, Khera N, Patel DR, Shen JF. Conjunctival subepithelial fibrosis and meibomian gland atrophy in ocular graft-versus-host disease. *Ocul Surf*. 2017;15:784–788.
16. 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;107:1343–1348.
17. Herretes S, Ross DB, Duffort S, 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;56:2348–2357.
18. Sakimoto T, Ohnishi T, Ishimori A. Significance of ectodomain shedding of TNF receptor 1 in ocular surface. *Invest Ophthalmol Vis Sci*. 2014;55:2419–2423.
19. Schargus M, Meyer-ter-Vehn T, Menrath J, Grigoleit GU, Geerling G. 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*. 2015;34:911–916.
20. Na KS, Yoo YS, Hwang KY, Mok JW, Joo CK. Tear osmolarity and ocular surface parameters as diagnostic markers of ocular graft-versus-host disease. *Am J Ophthalmol*. 2015;160. 143-149.e1.
21. Jung JW, Han SJ, Song MK, et al. Tear cytokines as biomarkers for chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:2079–2085.
22. Tibrewal S, Sarkar J, Jassim SH, et al. Tear fluid extracellular DNA: diagnostic and therapeutic implications in dry eye disease. *Invest Ophthalmol Vis Sci*. 2013;54:8051–8061.
23. He J, Ogawa Y, Mukai S, et al. In vivo confocal microscopy evaluation of ocular surface with graft-versus-host disease-related dry eye disease. *Sci Rep*. 2017;7:10720.
24. Pérez RL, Pérez-Simón JA, Caballero-Velazquez T, et al. Limbus damage in ocular graft-versus-host disease. *Biol Blood Marrow Transplant*. 2011;17:270–273.
25. Ogawa Y, Morikawa S, Okano H, et al. MHC-compatible bone marrow stromal/stem cells trigger fibrosis by activating host T cells in a scleroderma mouse model. *Elife*. 2016;5:e09394.
26. Yamane M, Ogawa Y, Mukai S, et al. Functional role of lacrimal gland fibroblasts in a mouse model of chronic graft-versus-host disease. *Cornea*. 2018;37:102–108.
27. Yaguchi S, Ogawa Y, Shimmura S, et al. Angiotensin II type 1 receptor antagonist attenuates lacrimal gland, lung, and liver fibrosis in a murine model of chronic graft-versus-host disease. *PLoS One*. 2013;8:e64724.
28. Mukai S, Ogawa Y, Urano F, Kudo-Saito C, Kawakami Y, Tsubota K. Novel treatment of chronic graft-versus-host disease in mice using the ER stress reducer 4-phenylbutyric acid. *Sci Rep*. 2017;7:41939.
29. Ogawa Y, He H, Mukai S, et al. Heavy chain-Hyaluronan/Pentraxin 3 from amniotic membrane suppresses inflammation and scarring in murine lacrimal gland and conjunctiva of chronic graft-versus-host disease. *Sci Rep*. 2017;7:42195.
30. Na KS, Yoo YS, Mok JW, Lee JW, Joo CK. Incidence and risk factors for ocular GVHD after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2015;50:1459–1464.
31. Arai S, Jagasia M, Storer B, et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria. *Blood*. 2011;118:4242–4249.
32. Uchino M, Ogawa Y, Uchino Y, Mori T, Okamoto S, Tsubota K. Comparison of stem cell sources in the severity of dry eye after allogeneic haematopoietic stem cell transplantation. *Br J Ophthalmol*. 2012;96:34–37.
33. Kamoi M, Ogawa Y, Uchino M, et al. Donor-recipient gender difference affects severity of dry eye after hematopoietic stem cell transplantation. *Eye (Lond)*. 2011;25:860–865.
34. Wang JC, 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;99:1514–1518.
35. Pathak M, Diep PP, Lai X, Brinch L, Ruud E, Drolsum L. Ocular findings and ocular graft-versus-host disease after allogeneic stem cell transplantation without total body irradiation. *Bone Marrow Transplant*. 2018;53:863–872.
36. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. *Ocul Surf*. 2017;15:539–574.
37. Curtis LM, Datiles 3rd MB, Steinberg SM, et al. Predictive models for ocular chronic graft-versus-host disease diagnosis and disease activity in transplant clinical practice. *Haematologica*. 2015;100:1228–1236.
38. Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea*. 2004;23:272–285.
39. Inamoto Y, Chai X, Kurland BF, et al. Validation of measurement scales in ocular graft-versus-host disease. *Ophthalmology*. 2012;119:487–493.
40. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010;128:94–101.
41. Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T. Psychometric properties and validation of the Standard Patient Evaluation of Eye Dryness questionnaire. *Cornea*. 2013;32:1204–1210.
42. Shimazaki J, Seika D, Saga M, et al. A prospective, randomized trial of two mucin secretogogues for the treatment of dry eye syndrome in office workers. *Sci Rep*. 2017;7:15210.
43. Tsubota K, Yokoi N, Shimazaki J, et al. New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. *Ocul Surf*. 2017;15:65–76.
44. Arita R, Minoura I, Morishige N, et al. Development of definitive and reliable grading scales for meibomian gland dysfunction. *Am J Ophthalmol*. 2016;169:125–137.
45. Murube J. Characteristics and etiology of conjunctivochalasis: historical perspective. *Ocul Surf*. 2005;3:7–14.

46. Schirra F, Höh H, Kienecker C, Ruprecht KW. Using LIPCOF (lid-parallel conjunctival fold) for assessing the degree of dry eye, it is essential to observe the exact position of that specific fold. *Adv Exp Med Biol*. 1998;438:853–858.
47. Németh J, Fodor E, Lang Z, et al. Lid-parallel conjunctival folds (LIPCOF) and dry eye: a multicentre study. *Br J Ophthalmol*. 2012;96:1380–1385.
48. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2015;21:984–999.
49. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18:348–371.
50. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125:606–615.
51. Finke J, Bethge WA, Schmoor C, et al. Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial. *Lancet Oncol*. 2009;10:855–864.
52. Luznik L, Bolaños-Meade J, Zahurak M, et al. High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease. *Blood*. 2010;115:3224–3230.
53. Ogawa Y, Kim SK, Dana R, et al. International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: proposed diagnostic criteria for chronic GVHD (Part I). *Sci Rep*. 2013;3:3419.
54. Rapoport Y, Freeman T, Koyama T, et al. Validation of International Chronic Ocular Graft-Versus-Host Disease (GVHD) Group diagnostic criteria as a chronic ocular GVHD-specific metric. *Cornea*. 2017;36:258–263.
55. Wolff D, Gerbitz A, Ayuk F, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. *Biol Blood Marrow Transplant*. 2010;16:1611–1628.
56. Carpenter PA, Kitko CL, Elad S, et al. 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*. 2015;21:1167–1187.
57. Inamoto Y, Martin PJ, Chai X, et al. Clinical benefit of response in chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2012;18:1517–1524.
58. Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood*. 1998;92:3098–3104.
59. Foss FM, DiVenuti GM, Chin K, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplant*. 2005;35:1187–1193.
60. Flowers ME, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*. 2008;112:2667–2674.
61. Perotti C, Del Fante C, Tinelli C, et al. Extracorporeal photochemotherapy in graft-versus-host disease: a longitudinal study on factors influencing the response and survival in pediatric patients. *Transfusion*. 2010;50:1359–1369.
62. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood*. 2006;108:756–762.
63. Kim SJ, Lee JW, Jung CW, et al. Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective, multicenter, phase II study. *Haematologica*. 2010;95:1935–1942.
64. Couriel DR, Saliba R, Escalón MP, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. *Br J Haematol*. 2005;130:409–417.
65. Johnston LJ, Brown J, Shizuru JA, et al. Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2005;11:47–55.
66. Busca A, Saroglia EM, Lanino E, et al. Mycophenolate mofetil (MMF) as therapy for refractory chronic GVHD (cGVHD) in children receiving bone marrow transplantation. *Bone Marrow Transplant*. 2000;25:1067–1071.
67. Busca A, Locatelli F, Marmont F, Audisio E, Falda M. Response to mycophenolate mofetil therapy in refractory chronic graft-versus-host disease. *Haematologica*. 2003;88:837–839.
68. Takami A, Mochizuki K, Okumura H, et al. Mycophenolate mofetil is effective and well tolerated in the treatment of refractory acute and chronic graft-versus-host disease. *Int J Hematol*. 2006;83:80–85.
69. Shimmura S, Ono M, Shinozaki K, et al. Sodium hyaluronate eyedrops in the treatment of dry eyes. *Br J Ophthalmol*. 1995;79:1007–1011.
70. Yamane M, Ogawa Y, Fukui M, et al. Long-term topical diquafosol tetrasodium treatment of dry eye disease caused by chronic graft-versus-host disease: a retrospective study. *Eye Contact Lens*. 2018;44(suppl 2):S215–S220.
71. Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A randomized, double-masked, placebo-controlled clinical trial of two forms of omega-3 supplements for treating dry eye disease. *Ophthalmology*. 2017;124:43–52.
72. Dry Eye Assessment and Management Study Research Group. n-3 Fatty acid supplementation for the treatment of dry eye disease. *N Engl J Med*. 2018;378:1681–1690.
73. Matsumoto Y, Dogru M, Goto E, et al. Autologous serum application in the treatment of neurotrophic keratopathy. *Ophthalmology*. 2004;111:1115–1120.
74. Ogawa Y, Okamoto S, Mori T, 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;31:579–583.
75. Leite SC, de Castro RS, Alves M, et al. Risk factors and characteristics of ocular complications, and efficacy of autologous serum tears after haematopoietic progenitor cell transplantation. *Bone Marrow Transplant*. 2006;38:223–227.
76. Rocha EM, Pelegrino FS, de Paiva CS, Vigorito AC, de Souza CA. GVHD dry eyes treated with autologous serum tears. *Bone Marrow Transplant*. 2000;25:1101–1103.
77. Zallio F, Mazzucco L, Monaco F, et al. A single-center pilot prospective study of topical application of platelet-derived eye drops for patients with ocular chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2016;22:1664–1670.
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;47:981–984.
79. Geerling G, Tost FH. Surgical occlusion of the lacrimal drainage system. *Dev Ophthalmol*. 2008;41:213–229.
80. Jacobs DS, Rosenthal P. Boston scleral lens prosthetic device for treatment of severe dry eye in chronic graft-versus-host disease. *Cornea*. 2007;26:1195–1199.
81. Takahide K, Parker PM, Wu M, et al. 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*. 2007;13:1016–1021.
82. Inamoto Y, Sun YC, Flowers ME, et al. Bandage soft contact lenses for ocular graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:2002–2007.
83. Magro L, Gauthier J, Richet M, et al. Scleral lenses for severe chronic GvHD-related keratoconjunctivitis sicca: a retrospective study by the SFGM-TC. *Bone Marrow Transplant*. 2017;52:878–882.
84. Korb DR, Blackie CA. Using goggles to increase periocular humidity and reduce dry eye symptoms. *Eye Contact Lens*. 2013;39:273–276.
85. Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye Contact Lens*. 2003;29:96–99.
86. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. *Cornea*. 2006;25:171–175.
87. Frucht-Pery J, Sagi E, Hemo I, Ever-Hadani P. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol*. 1993;116:88–92.
88. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology*. 2000;107:631–639.
89. Wang Y, Ogawa Y, Dogru 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.
90. Robinson MR, Lee SS, Rubin BI, et al. Topical corticosteroid therapy for cicatricial conjunctivitis associated with chronic graft-versus-host disease. *Bone Marrow Transplant*. 2004;33:1031–1035.
91. Abud TB, Amparo F, Saboo US, et al. A clinical trial comparing the safety and efficacy of topical tacrolimus versus methylprednisolone in ocular graft-versus-host disease. *Ophthalmology*. 2016;123:1449–1457.
92. 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.
93. Kheirkhah 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.
94. Ogawa Y, Dogru M, Uchino M, et al. Topical tranilast for treatment of the early stage of mild dry eye associated with chronic GVHD. *Bone Marrow Transplant*. 2010;45:565–569.
95. Amparo F, Dastjerdi MH, Okanobo A, et al. Topical interleukin 1 receptor antagonist for treatment of dry eye disease: a randomized clinical trial. *JAMA Ophthalmol*. 2013;131:715–723.
96. Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: results of a phase III, randomized, double-masked, placebo-controlled trial (OPUS-3). *Ophthalmology*. 2017;124:53–60.

97. Peris-Martínez C, Menezo JL, Díaz-Llopis M, Aviñó-Martinez JA, Navea-Tejerina A, Risueño-Reguillo P. Multilayer amniotic membrane transplantation in severe ocular graft versus host disease. *Eur J Ophthalmol*. 2001;11:183–186.
98. 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;105:334–339.
99. Meller D, Fuchsluger T, Pauklin M, Steuhl KP. 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*. 2009;28: 233–236.
100. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825–828.