



Published in final edited form as:

Biol Blood Marrow Transplant. 2019 February ; 25(2): e46–e54. doi:10.1016/j.bbmt.2018.11.021.

Ocular graft-versus-host disease 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

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Conflict-of-interest statement: There are no conflicts of interest to disclose.

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Abstract

Ocular graft-versus-host disease (GVHD) occurs in more than half of patients who develop chronic GVHD after allogeneic hematopoietic cell transplantation (HCT), causing prolonged morbidity which affects activities of daily living and quality of life. Here we provide an expert review of ocular GVHD in a collaboration between transplant 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 in this review. Ocular GVHD has at least three biological processes: lacrimal gland dysfunction, meibomian gland dysfunction, and corneconjunctival inflammation. Preclinical models have found several novel pathogenic mechanisms including renin angiotensin system and endoplasmic reticulum stress signaling that can be targeted by therapeutic agents. Many studies have identified reliable tests for establishing diagnosis and response assessment of ocular GVHD. Efficacy of systemic and topical treatment for ocular GVHD is summarized. It is important for all health professionals taking care of HCT recipients to have adequate knowledge of ocular GVHD for optimal care.

Keywords

chronic graft-versus-host disease; eye; review; biology; treatment; hematopoietic cell transplantation

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 transplant survivors, compromising both quality of life (QOL) and function.¹ Ocular involvement is common in patients with chronic GVHD, occurring in more than fifty percent.²⁻⁵ Since the ocular surface can be evaluated by physicians and ophthalmologists, it is important for all health professionals taking care of 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 transplant 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 described previously⁶ to reflect the strength of recommendations and the quality of evidence supporting them (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 called, dry eye^{7, 8} which typically develops by six to nine months after allogeneic HCT.^{3, 9} Symptoms of ocular GVHD include irritation, burning, pain, redness, photophobia, blurry vision, excessive tearing and the sensation of having sand or grit in the eyes.^{9, 10} Besides dry eye, conjunctival injection is another important sign of ocular GVHD that can easily be recognized by any health professional.

Pathophysiology

The tear film is composed of three layers: aqueous, lipid and mucin. The 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 quick 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 has at least three important biological processes: lacrimal gland dysfunction, meibomian gland dysfunction, and corneconjunctival inflammation. As with chronic

GVHD in 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 mediumsized 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 gland, and lymphocytic infiltration of the lacrimal gland.¹⁴ T cells are mainly detected 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 allo-immune response to ductal epithelium.^{13, 17}

Tear film osmolality and the level of cytokines including IL-6, IL-8, IL-17, IFN- γ , TNF- α and chemokines such as CXCL8 and CXCL10 in tear fluid are elevated in ocular GVHD because of reduced tear production, increased 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 subbasal nerve of the central cornea and limbal region,²³ proving that immune-competent cells infiltrate into avascular corneal lesions in ocular GVHD.

Preclinical models

There are several murine models of ocular GVHD.^{17, 24, 25} In vitro analysis has shown that fibroblasts derived from GVHD-involved lacrimal glands have highly proliferative, invasive, and migration characteristics.²⁶ Murine models showed 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, reduction of regulatory T cells, and increased Th17 effector T cells similar to autoimmune pathological 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 pathological 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 gland 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 is a complex purified from human amniotic membrane, known to exert anti-inflammatory and anti-scarring actions, and reduced gene expression of collagen type I, collagen type III and NF- κ B in murine lacrimal glands affected by GVHD.²⁹

Incidence

The incidence of ocular GVHD varies widely in published literature, partly due to different diagnostic criteria. In a single-center study of 172 patients,¹⁰ ocular GVHD was defined as a new onset of at least two of five parameters (i.e., new onset of dry-eye symptoms, tear break up time < 5 seconds, Schirmer I < 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 includes the Schirmer test.³⁰ In a prospective multicenter study of patients with chronic GVHD (diagnosed according to the 2005 NIH criteria), eyes were the third most commonly involved organ, affecting 51% of patients at the time of chronic GVHD diagnosis. A 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 showed that prior acute GVHD,^{10, 30} use of peripheral blood stem cells,^{30, 32} and HCT from a female donor to a male recipient^{10, 33} are associated with ocular GVHD. A single retrospective study identified that absence of antithymocyte globulin prophylaxis, more organs involved with GVHD, non-Caucasian patients, and EBV-seropositive donors are associated with ocular GVHD.^{30, 34}

Evaluation measures

Evaluation of ocular GVHD includes measures that can be used by hematologists in the clinics and more specialized measures used by ophthalmologists. Recommendation levels are summarized separately for diagnosis and response measures in Table 3.

Schirmer test: tear volume assessment

The Schirmer test without anesthesia is a standard method of assessment. The Schirmer test 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 length of wetting after a period of 5 minutes. Administering the test with the eyes closed may minimize the variability of results. Diagnostic cut-off values have been proposed from 5 to 10 mm in 5 minutes, and the Schirmer test has shown more than 80% diagnostic sensitivity and specificity for ocular GVHD.^{20, 35-37} The Schirmer test, however, is inaccurate, variable, not inclusive of the evaporative aspect of dry eye, and has poor correlations with others tests and treatment response.^{38, 39}

Ocular surface disease index (OSDI): ocular symptoms assessment

Several questionnaires have been used in clinical trials to document dry-eye related symptoms, including OSDI,⁴⁰ the Standard Patient Evaluation of Eye,⁴¹ and the Dry Eye-Related Quality-of-Life Score.⁴² Among them, OSDI is commonly used worldwide. OSDI

consist of 12 patient-reported questions related to dry eyes, and is a valid and reliable instrument for measuring dry eye disease.⁴⁰ A study has shown 44% sensitivity and 98% specificity for OSDI in the diagnosis of ocular GVHD.³⁵ Its utility as a response measure has been shown in a prospective multicenter study.³⁹

Corneal staining: corneal surface integrity assessment

Fluorescein, a vital dye for staining the ocular surface, is extensively used for diagnosis and management of dry eye disease. It can be used to stain damaged epithelium of both the cornea and conjunctiva. Fluorescein is commonly used to evaluate the degree of corneal epitheliopathy. Lissamine Green and Rose Bengal are also used for some grading criteria of dry eye disease. Instilled dye staining indicates ocular surface disease, with greater staining showing greater severity of dry eye disease.³⁶ For evaluating and grading staining, there are several methods including the 1995 National Eye Institute/Industry Workshop system, area-density combination index, the Oxford staining score, and the Ocular Staining Score by the Sjogren's International Collaborative Clinical Alliance.³⁶ Disruption in superficial cell tight junctions or defective glycocalyx causes damage to epithelial cells and staining by fluorescein dye. One study showed that the sensitivity and specificity of corneal staining for diagnosis of ocular GVHD were 91% and 54%, respectively.³⁵

Tear film breakup time (TBUT): tear film stability assessment

The tear film breakup time (TBUT) is a standard measure for dry eye diagnosis and treatment response.⁴³ It is the interval of time that elapses 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 three times and then to cease blinking. The cut-off time for dry eye diagnosis ranges from less than 10 seconds to less than 5 seconds. It is important to use a controlled volume of fluorescein such as 2 μ l for standardized measurement.³ One study showed that the sensitivity and specificity of TBUT for diagnosis of ocular GVHD were 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 of the lid margin or meibomian glands, although their utilities have not been validated well in ocular GVHD. One study showed the utility of the meibomian gland plugging score (0 = none; 1 = 1-2 glands; 2 = 2-3 glands; 3 = all 5 glands, lid margin swelling) for diagnosis of ocular GVHD.³⁷

Lid-parallel conjunctival folds (LIPCOF)

Conjunctivochalasis or lid-parallel conjunctival folds (LIPCOF) are bulbar conjunctival folds that sit on top of the lower eyelid margin and can be observed by using a slit lamp. Grading of the extent of conjunctival folds as a sign of dry eye syndrome has been proposed by several investigators.^{45, 46} The most widely used grading is the Höh's scheme, which is a simple, noninvasive diagnostic test for dry eye diseases.⁴⁶ LIPCOF is graded from 0 (no folds) to 3 (pronounced folds) and is measured above the temporal part of the lower eyelid.

Caveats to its usefulness are its subjectivity and inability to distinguish between hyposecretive and hyperevaporative dry eyes. A multicenter study showed that LIPCOF test had moderate sensitivity and specificity, and had 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 in order 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 around 3 months after HCT and the mean value of Schirmer tests decreased to 10 mm at 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 ophthalmological screening evaluation at 3 months and at 12 months after HCT, as well as at the time of initial diagnosis of chronic GVHD of any sites.⁵⁰

No specific prevention strategies are established except for prevention of chronic GVHD by T cell depletion, such as antithymocyte globulin, post-transplant cyclophosphamide and CD34 selection.^{51, 52} The efficacy of cyclosporine eye drops for prevention of ocular GVHD is under investigation in a randomized phase III study (NCT00755040).

Diagnosis, staging and response criteria

The 2014 NIH criteria define a simple symptom-based diagnosis of ocular GVHD,⁷ where 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 zero to three, 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 given for the use of lubricant eye drops less than 3 times a day with no need for punctal plugs and no impact on ADL. A score of 3 is given for the inability to work or the loss of vision due to KCS or the need for special eyewear.⁷ All other moderately symptomatic situations are scored with 2 points. The NIH eye score combined with the Schirmer test shows more than 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 while 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 OSDI.³⁹

In 2013, the International Chronic Ocular GVHD Consensus Group (ICOGCG) proposed new diagnostic metrics in order to increase objectivity in diagnosis and follow-up of chronic GVHD.⁵³ Measures are obtained by ophthalmologic exams of the Schirmer test without anesthesia, corneal staining and conjunctival injection, and patient-reported dry eye symptoms (i.e., OSDI). The presence of systemic chronic GVHD is also taken into account and a higher score is required to diagnose probable ocular GVHD in patients without involvement of other organs.⁵³ One study compared diagnostic utility between the 2005 NIH

criteria and the ICOGCG criteria and 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 particularly in severer cases of ocular GVHD.⁵⁴ Further validation of the ICOGCG score, in particular for 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 causing toxicities.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. Recommendation levels of treatment for ocular GVHD are summarized in Table 4. Mild ocular GVHD may be often treated with topical therapies.^{55, 56}

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 patients' overall conditions, comorbidities and risk of recurrent malignancy into account.^{7, 55} A multicenter prospective observational study showed that 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 mostly including corticosteroids and calcineurin inhibitors.⁵⁷

Data on the efficacy of individual systemic treatments specifically for ocular GVHD are limited, but response rates are reported as a secondary endpoint in several prospective studies. 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 mofetil⁶⁶⁻⁶⁸ in a corticosteroid-refractory setting. These response rates should be interpreted with great caution due to the small number of cases, different response criteria, and different assessment timing applied in each study.

Increase of ocular surface moisture

Intense lubrication is important to preserve the integrity of the ocular surface, diminishing lid-ocular surface friction, hence 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, avoid epithelial damages 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 (diquafosol and rebamipide) are effective for 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 since they contain epitheliotrophic growth factors, cytokines, nerve growth factors, tissues inhibitors of matrix metalloproteinases and

complement factors.⁷³⁻⁷⁶ Autologous serum eye drops have to be prepared according to local regulations for blood products, are contraindicated for patients with active infections, and can be difficult to prepare in anemic patients. A prospective pilot study of 26 patients showed that platelet-derived eye drops improved ocular symptoms in 91% of patients and improved objective findings in 32% of patients.⁷⁷

Control of evaporation

Punctal occlusion with collagen or silicone plugs is helpful to sustain 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 for some patients.⁷⁹ Scleral contact lenses are effective in ameliorating symptoms in patients with severe ocular GVHD and are able to improve QOL dramatically 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 of ocular surface inflammation

Randomized studies have shown that cyclosporine eye drops improve the Schirmer test results and tear film breakup time, increase the number of conjunctival goblet cells, and reduce 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 for those without visible inflammation but with underlying inflammatory processes.⁸ The recommended dose of cyclosporine eye drops in chronic GVHD is 0.05% or 0.1% 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 seem to be associated with a lower risk for development of secondary glaucoma compared with prednisolone acetate.⁸

A phase I/II prospective, randomized, double-blinded study showed that topical tacrolimus 0.05% was safe, well tolerated, and effective for ocular GVHD without the hypertensive effects of topical corticosteroids.⁹¹ Topical 0.02% tacrolimus ointment also exhibits rapid anti-inflammatory effects in patients with ocular GVHD and allows 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 β .⁹⁴ Topical anakinra 2.5%, an interleukin-1 receptor antagonist improved symptoms and corneal epitheliopathy of dry eye disease after 12 weeks of administration.⁹⁵ Topical lifitegrast, an integrin antagonist inhibiting LFA-1/ICAM-1 interaction, is a new FDA-approved treatment for dry eye disease.⁹⁶ In a randomized, placebo-controlled phase I/II study (NCT02975557), brimonidine eye drops showed a reduction in ocular redness and discomfort after 3 months of treatment. The efficacy of nanoemulsion eye drops of brimonidine is currently tested in a phase III study (NCT03591874). Topical treatment is usually continued 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 for promoting 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 (i.e., corneal transplantation) have been reported in patients with ocular GVHD but have been less beneficial in cases 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 future recommendations

Ocular GVHD can cause prolonged morbidity affecting ADL and QOL. Timely diagnosis and early treatment of ocular GVHD is warranted to protect vision and to avoid severe complications such as corneal ulceration and perforation. Care of patients with ocular GVHD warrants close collaboration between the transplant physicians and ophthalmologists.

Future research should be directed towards establishing reliable and widely-available tools for diagnosis and response measurement of ocular GVHD. Distinguishing active inflammation from its sequelae is important, but has not been addressed in current criteria. Several signs such as pseudomembrane, limbal stem cell deficiency, cornea neovascularization, cornea conjunctivalization, nasolacrimal duct obstruction, severe conjunctival injection, corneal perforation, and LIPCOF may help to distinguish active inflammation. Additionally, 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 in this paper, preclinical models show that inflammation, immune dysregulation, and fibrosis are also implicated in ocular GVHD.^{15, 17, 23, 24, 26} Many 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

CIBMTR Support List

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 (NIAID); a Grant/Cooperative Agreement 4U10HL069294 from NHLBI and NCI; a contract HSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-17-1-2388 and N0014-17-1-2850 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals, Inc.; *Amgen, Inc.; *Amneal Biosciences; *Angiocrine Bioscience, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US; Atara Biotherapeutics, Inc.; Be the Match Foundation; *bluebird bio, Inc.; *Bristol Myers Squibb Oncology; *Celgene Corporation; Cerus Corporation; *Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd.; Gilead Sciences, Inc.; HistoGenetics, Inc.; Immucor; *Incyte Corporation; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals, Inc.; Juno Therapeutics; Karyopharm Therapeutics, Inc.; Kite Pharma, Inc.; Medac, GmbH; MedImmune; The Medical College of Wisconsin; *Mediware; *Merck & Co, Inc.; *Mesoblast; MesoScale Diagnostics, Inc.; Millennium, the Takeda Oncology Co.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; *Neovii Biotech NA, Inc.; Novartis Pharmaceuticals Corporation; Otsuka Pharmaceutical Co, Ltd. – Japan; PCORI; *Pfizer, Inc.; *Pharmacyclics, LLC; PIRCHE AG; *Sanofi Genzyme; *Seattle Genetics; Shire; Spectrum Pharmaceuticals, Inc.; St. Baldrick's Foundation; *Sunesis Pharmaceuticals, Inc.; Swedish Orphan Biovitrum, Inc.; Takeda Oncology; Telomere Diagnostics, Inc.; and University of Minnesota. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

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- Recent knowledge of ocular GVHD is reviewed by expert transplant physicians and ophthalmologists.
- Biological processes include lacrimal and meibomian gland dysfunction and corneconjunctival inflammation.
- Renin angiotensin system and endoplasmic reticulum stress signaling are implicated in murine models.
- The NIH eye score, Schirmer test and corneal staining are useful for diagnosis of ocular GVHD.
- Emerging treatments for dry eye disease (anakinra, lifitegrast etc.) may be tested for ocular GVHD.

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 one properly randomized, controlled trial.
II	Evidence for at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from more than one center) or from multiple time-series or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive.

Table 2.

Risk factors associated with the onset of ocular GVHD

Risk factor
Prior 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
EBV-seropositive donor ³⁴

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Table 3.

Evaluation measures of 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}
Ocular surface disease index (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}
Tear film breakup time (TBUT)	B-II ^{35, 37}	B-III
ICOGCG score	B-II ^{35, 54}	C-III
Meibomian score [†]	B-II ³⁷	C-III
Lip-parallel conjunctival folds (LIPCOF)	C-II ⁴⁷	C-III

* Oxford grand total score.

[†] Meibomian glands plugging: 0 = none; 1 = 1-2 glands; 2 = 2-3 glands; 3 = all 5 glands, lid margin swelling.³⁷

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 months 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.