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CHRONIC OCULAR GRAFT VERSUS HOST DISEASE: AN UPDATE AND REVIEW

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ABSTRACT

An updated comprehensive literature review was completed of chronic ocular graft versus host disease (oGVHD) to identify current and future considerations as to the causes, diagnosis, and treatment of this complication after allogenic hematopoietic cell transplantation (HCT). Graft-versus-host disease involves multiple organ systems, including the eye, and is a leading cause of mortality and morbidity in these patients. This review consisted of a comprehensive search of PubMed, ClinicalTrials.gov and NIH.gov databases.

oGVHD is a debilitating and potentially sight-threatening condition. Commonly involved ocular structures include the cornea, conjunctiva, meibomian glands, eyelids, lacrimal gland, and tear film. Identifying and treating the ocular complications at the early stages may improve the outcomes and quality of life in these patients. Aggressive lubrication, preservation of tear film and inflammation control, including minimizing surface scarring, are treatment goals. Co-management with HCT and other pertinent health care providers is critical for early diagnosis and to initiate prompt therapy to minimize ocular damage. Stepped therapy, including the use of emerging systemic treatments, can be useful in the management of oGVHD with stable visual function, quality of life and complication management as goals of treatment.

Key Words: dry eye, ocular graft versus host disease (oGVHD), filamentary keratitis, hematopoietic allogeneic stem cell transplant, cytokines

The first bone marrow transplantation (BMT) was performed by E. Donnall Thomas in 1956, a future Nobel Prize winner, between identical twins for treatment of acute leukemia.[1] Thomas and others continued to research and refine BMTs, eventually developing procedures and treatments that use non-sibling donors, and by 2016 over 400,000 allogeneic related blood transplantations had been performed worldwide.[2–5] Currently, more than 50,000 transplants are carried out annually worldwide (WHO website). Despite the overall advancement in procedures and outcomes, graft versus host disease (GVHD), both acute and chronic forms, remains a significant complication. Acute GVHD develops typically within the first 100 days of transplantation, while chronic GVHD occurs after three months. There is also an overlap between acute and chronic. It is estimated that between 28–37% of HCT recipients develop chronic GVHD.[6] Of these patients, 40–60% will have ocular complications and although any structure can be impacted, the ocular surface and adnexa are the most commonly involved.[7] Frequent anterior segments conditions include keratitis sicca, meibomian gland dysfunction, cicatricial conjunctival fibrosis, sclerodermatous lid atrophy, and filamentary keratitis.[8–12]

Ocular symptoms do not typically appear in isolation and are found in conjunction with other systemic concerns, involving the mouth, skin, lungs or liver.[12] Ocular complaints usually present as blurred vision, ocular discomfort, increased tearing and mucous discharge.[13,14] While the ocular findings are not life-threatening, the impact on the quality of life and activities of living can be quite severe.[15] Since the transplant team will be the first to hear these complaints, the need to recognize the early symptoms oGVHD and to initiate a proper referral for an ophthalmic evaluation are critical.

Diagnosis is based on clinical examination, including biomicroscopy, measurement of tear production and stability, and the application of vital stains. The National Institute of Health proposed guidelines in 2005 that aids in the diagnosis of chronic oGVHD.[16] Criteria suggested for a new diagnosis of chronic oGVHD include either (1) low Schirmer test values with a mean value of both eyes less than 5 mm at 5 minutes or (2) a new onset of corneal epithelial defects with mean values of 6 to 10 mm on the Schirmer test, is sufficient for the diagnosis of chronic oGVHD if accompanied by distinctive manifestations in at least 1 other organ. Likewise, the International Chronic Ocular GVHD Consensus Group developed criteria in 2013 to more accurately assess the presence of oGVHD.[11] This group identified four variables to measure in patients following HCT: Ocular Surface Disease Index (OSDI) questionnaire, Schirmer's score without anesthesia, corneal staining, and conjunctival injection. Variables are scored and totaled for a composite grading. The presence or the absence of systemic GVHD is also included as a factor. Patients then are given a diagnostic category of either no, probable or definite chronic oGVHD. The updated 2013 criteria established by the International Chronic GVHD Consensus Group using best clinical practice was subsequently validated with further study, particularly in severe GVHD.[17] While used primarily for consistently evaluating findings in research trials, the adoption of these criteria is not universally used clinically. Additionally, as technological advances continue to develop, the use of ocular surface parameters is becoming more routine as objective testing becomes more available in clinical practice.[18–21]

OVERVIEW OF CGVHD

Mathé and associates in 1967 reported on the lethal complications of graft-versus-host, which they called "secondary syndrome", following allogeneic transplantations.[22] They stated that of the 15 successful grafting cases, all developed this syndrome which was fatal in 11 patients. Over the next 30 years, cGVHD has remained the leading cause of non-relapse mortality in patients who have survived longer than 2 years.[23] Despite advances in research, cGVHD appears to be increasing and ophthalmic practitioners are likely to encounter patients with ocular concerns.[6] It is believed that the risk of developing cGVHD has several factors, including mismatched or unrelated donors, female donors to male recipients, using older donors and transplants using mobilized peripheral blood stem cell as a graft source.[24–27]

Unlike acute GVHD, which is characterized by a "cytokine storm," or a fulminant inflammatory response between donor lymphocytes and damaged host cells, the pathogenesis of cGVHD is less understood.[28] It is believed to be like an autoimmune response that eventually involves multiple organs. Zeiser and Blazer recently reviewed the biological events leading to the development of cGVHD[29] and described a three-phase process in-volving tissue damage from the cytotoxic conditioning regimen to the gut epithelium. This allows pathogens to translocate into the cells, triggering T cell activa-tion, thus priming the graft-versus-host reaction. The next phase involves both an alloreactive B cell and T cell response that stimulates helper T cells, causing the release of inflammatory cytokines. Concurrently, the thymus is not able to regulate the inflammatory response due to conditioning damage and alloreactive T cell-induced injury. The last phase is character-ized by fibroblast proliferation, extracellular matrix production and immunoglobulin deposition in tissue, causing damage and fibrosis.

In 2015, a series of papers affirmed the 2014 NIH Chronic GVHD Consensus Conference findings.[30–35] This conference helped to standardize the definitions and features of cGVHD for research and clinical studies. Diagnosis requires at least one clinical manifestation or biopsy-proven signs involving the skin, mouth, GI tract, lung, fascia, and genitalia. Interestingly, the

ocular signs of cGVHD are not enough in of themselves for a diagnosis, since many of them overlap with other conditions, including keratitis sicca and meibomianitis. Reduced tear production by Schirmer's test strips is considered only as a "confirmatory" test when other signs of cGVHD are present. The global severity of cGVHD is calculated as mild, moderate or severe.[36] In a prospective study by Arora, et al, the onset of cGVHD was 19% mild, 53% moderate and 28% severe.[37] The higher the severity score, the greater the chance of mortality.[38]

Prevention of cGVHD is considered during the pre-transplant conditioning phase and after transplant subsequently with the use of prophylaxis medications. The key consideration in all HCT is to have an HLA-match recipient using high-resolution typing. Conditioning regimens are a combination of chemotherapy, irradiation, and lymphotropic antibodies to promote donor cell engraftment. These regimens can be classified as myeloablative or reduced-intensity according to the dose and its effect in the bone marrow. Myeloablative, or higher intensity regimens rely on high treatment doses to control the malignancy and the graft versus tumour effect from the donor's immune system. Reduced-intensity conditioning regimens rely more on graft versus tumour effect. In terms of clinical uses, myeloablative regimens have a higher rate of organ toxicities and thus used preferentially to treat patients younger than age 65. Reduced-intensity regimens carry less organ toxicity risk and thus used in older patients. The risk of cGVHD is similar between different regimen intensities.[39] Regarding ophthalmic complications, irradiation containing conditioning regimens are associated with higher rates of cataracts, but not oGVHD. In fact, in a recently published long-term study, the follow up of 96 patients who received HCT under age 30, lead to the belief that damage related to oGVHD occurs with both conditioning regimens with or without irradiation.[40] Immunosuppression therapy post-graft with the antimetabolite methotrexate, and T cell activation inhibitors such as cyclosporine or tacrolimus is the most common approach to prevent GVHD.[41] Although methotrexate and calcineurin inhibitor combinations significantly reduce the risk of acute GVHD, it has little effect on the development of chronic GVHD. Approaches to decrease the risk of chronic GVHD include the use of anti-thymocyte globulin before transplant, the use of high dose cyclophosphamide post-transplant or ex-vivo T-cell depletion.[42]

Treatment of cGVHD depends on the severity, but often includes the use of corticosteroids as first-line therapy.[43] However, about 50% of patients will develop steroid-dependent or steroid-resistant cGVHD.[44] Common secondary pharmaceutical treatments include tacrolimus or sirolimus, cyclosporine A and mycophenolate mofetil. Supportive treatment to prevent infection is also an important adjunct and many patients are on antiviral and antifungal medications.

The monoclonal antibody, rituximab, has been used in the management of steroid-refractory cGVHD and targets pathogenic B cells that express the protein CD20, reducing the immunity response.[45] Rituximab is effective, but remnant alloreactive B cells persist after treatment discontinuation.[46] Teshimi, et al reported that rituximab is more effective in early cGVHD, primarily on the musculoskeletal and cutaneous concerns, and has less of a response in severe cases, including the ocular complications.[47] Several studies have shown that rituximab can variably reduce the ocular manifestations between 13–38%.[48,49]

Ibrutinib was recently approved as a second-line treatment for corticosteroid refractory cGVHD. It belongs to a class of drugs known as Bruton's tyrosine kinase (BTK) inhibitors. BTK proteins are B cell signalers. Ibrutinib also inhibits interleukin-2–inducible T-cell kinase, a T cell regulator.[50] Clinical trials showed ibrutinib to reduce the severity and progression in 71% of responders at least 20 weeks.[50,51] Ibrutinib also showed that patients who responded were able to reduce the corticosteroid dosage at least 50% on average. There has been little evidence that oGVHD responds to the use of ibrutinib.

Ruxolitinib has been described as a promising second-line therapy for cGVHD and is a JAK1/2 inhibitor. Janus kinases (JAK) are protein kinases that signal cytokines and play a role in the activation of several immune cell types in cGVHD pathogenesis.[52] Reported overall response rate with ruxolitinib has been reported to be from 43–85%.[53–56] Khoury, et al, in a small study of 19 patients, showed partial resolution of chronic oGVHD in 100% of patients.[54] Currently,

the REACH trials, a three-phase prospective study, is studying the effectiveness of ruxolitinib versus best available therapy in a patient with steroid-refractory GVHD after BMT.[31,57] The most common side effects from the use of ruxolitinib include reactivation of CMV infection and cytopenia.[56,58] There is also a small risk of relapse compared to other therapies.[56]

Another second-line therapy that is used in conjunction with immunosuppressives is extracorporeal photopheresis (ECP), especially in the cutaneous and mucosal manifestations,[59] ECP may also be useful in as a first-line therapy in patients that have contraindications to immunosuppressives such as cerebral toxoplasmosis.[60] While the mode of action is unclear, the combination of leukapheresis and photodynamic therapy has been reported to help to moderate the effects of GVHD. A multicenter trial, with results reported in 2018, showed that ECP had a 62% provider response rate and a 44% NIH criteria response rate.[61] The study also showed that most patients reduced the dosage of prednisone after ECP. There also appears to be no significant long-term major side effects.[62] The eyes were included as target organs, but the ocular impact separate from other organ involvement was not discussed. Malik, et al, reported an overall response rate for ocular involvement of 60%.[63]

OVERVIEW OF CHRONIC oGVHD

There have been many excellent reviews of chronic oGVHD written over the last several decades, with improvements in both the understanding and management of this unfortunate ocular complication.[7,9,11,14,64–67] One of the first reviews was by Franklin, et al in 1983,[68] who described the spectrum of chronic oGVHD that we still see in clinical practice today. Keratoconjunctivitis sicca was the main finding then, along with stromal ulceration, cicatricial lagophthalmos, and uveitis. These ocular complications were thought to be a combination of toxic drug effects and the graft-versus-host response. A more recent review discussed chronic oGVHD, including the impact on the quality of life and is a collaboration between the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the Transplant Complication Working Party of the European Society of Blood and Marrow Transplantation (EBMT).[67] It includes both transplant providers and ophthalmic practitioners and is focused on evidenced-based recommendations.

Due to non-standardized criteria, the incidence of oGVHD is quite varied, with estimates between 10–60%.[10,14,64,66–75] Na, et al, reported in a retrospective study of 635 patients, an incidence of 1.33% for acute oGVHD and 33.33% for chronic oGVHD.[10] Risk factors for chronic oGVHD have been reported to include prior acute GVHD, peripheral stem cells, female donor to male recipient, and more than 2 organs affected.[10,67,76–78] Wank, et al, also found that non-Caucasian and EBV-seropositive donors have a higher risk to develop oGVHD.[12] Berchici, et al prospectively evaluated hematopoietic stem cell transplant patients using both the NIH and International Chronic Ocular GVHD Consensus group criteria for 24 months and found a strong association between systemic GVHD and the development of oGVHD.[79] They found greater than 50% of patients developed chronic oGVHD after allogeneic stem cell transplant and the typical time to diagnosis is within 36 months.

Giannaccare, et al showed that dry eye is already present in a large percentage of patients with hematologic disease before HCT.[80] Early diagnosis is key to control of symptoms and ultimately managing the clinical signs. Recent research is focused on advancements in prophylaxis, diagnostic criteria, and treatment. Another study also by Giannaccare, et al showed that oGVHD alters the biomechanical properties of the cornea, such as corneal hysteresis, possibly through collagen stromal fibril changes. Measuring corneal hysteresis may improve the severity grading accuracy of oGVHD, as corneal biomechanical changes are closely associated with ocular surface inflammation.[81]

Arafat, et al found elevated levels of neutrophil elastase, MMP-8 (matrix metalloproteinase) and MMP-9 and myeloperoxidase in tears of patients with oGVHD.[82] Also, certain proteins neutrophil extracellular traps (NET) and NET associated proteins are seen with the ocular surface desiccation, fibrotic eyelid changes and persistent inflammation in oGVHD.[83] These proteins may not only be helpful diagnostic biomarkers but also lead to future treatments reversing these effects.

Another possible diagnostic and monitoring aid may be the use of anterior segment optical coherence

tomography to monitor the amount of higher-order aberrations, an objective measure of visual function.[84] The use of in-vivo confocal microscopy is beneficial for both early diagnosis and monitoring of cell changes, inflammation and disease severity of oGVHD patients, although not readily clinically available.

As noted previously, the most common ocular findings include keratitis sicca, mucoid conjunctivitis, sclerodermatous-like fibrosis of the eyelids and persistent corneal defects (Figure 1 and 2).

Tear film dysfunction is typically the first manifestation and involves a deficiency of all the three tear layers.[67,85,86] This "mixed" dry eye is considered the key finding in chronic oGVHD resulting in aqueous deficient and evaporative dry eye.[14,85,87] Of interest, HCT patients without systemic GVHD do not regularly develop dry eye disease.[86] Conjunctival injection is the second most common sign.

FIG. 1 Diffuse punctate keratitis with filament formation.

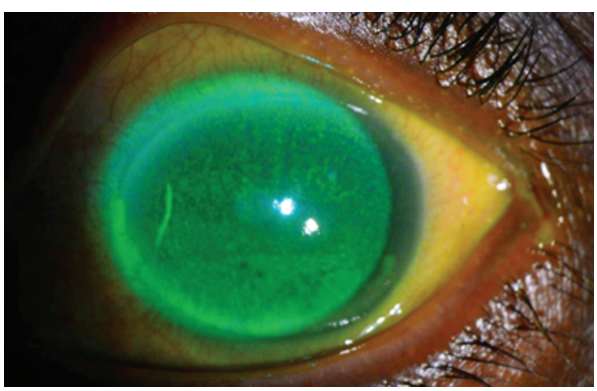
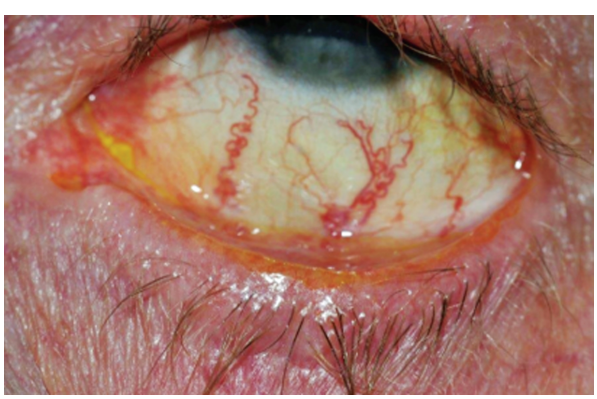


FIG. 2 Common findings including conjunctival injection, meibomianitis and lid fibrosis.



As with other target organs, the initial inflammatory cascade is likely a T cell-mediated process.[88–90] This causes fibrotic changes in the lacrimal ducts and the meibomian glands.[91,92] A cGVHD animal model developed by He, et al demonstrated increased inflammatory cell deposition in the conjunctiva and eyelids, increased fibroblasts and greater accumulation of collagen bundles.[93] The density of conjunctival goblet cells was decreased as well as the number of microvilli. The corneal limbal stem cells show increased apoptosis with resulting epithelial atrophy.[94] Confocal microscopy studies found microstructural alterations in all layers of the cornea as well as increased density of the dendritic cells and globular immune cells indicating increased inflammation.[95] The morphology of the sub-basal nerves was altered in oGVHD patients with increased tortuosity and branching.[96]

No widely accepted methods of suscepti-bility testing for biomarkers currently exist for early oGVHD. Tear film osmolarity (TFO) has been reported to be increased in chronic oGVHD, but it is unclear to what degree and how this reflects the progression of the disease. Most studies have had subjects that have been on systemic immunosuppression or topical therapy.[21,97] Increased TFO best correlated with a decrease in TBUT, but less with Schirmer values and the OSDI questionnaire. TFO has not been shown to correlate with corneal or conjunctival staining. TFO does moderately correlate with the disease score of the International Chronic Ocular Graft-Versus-Host-Disease Consensus Group.[11] With further study, TFO may be a useful point-of-care test to use in post-HCT patients to diagnose chronic oGVHD. MMP-9 is significantly increased in ocular surface stress and desiccation may be clinically evaluated. The sensi-tivity of 85% and specificity of 94% was shown in the rapid point-of-care clinical diagnostic test (98). InflammaDry® successfully identified inflammation in 40% of established dry eye patients.[99] Results also correlate well with additional testing such as OSDI and meibomian gland pathologic changes. This may be of significant benefit to early identification and future monitoring of high-risk patients.

Conjunctival biopsy has been used previously to demonstrate changes in the conjunctival tissue including a decrease in goblet cells, atrophy of the

epithelium and scattered lymphocytes.[70,100] However, this was impractical, invasive and therefore was not clinically adopted. Eberwein suggested that impression cytology may be used to detect CD8-positive lymphocytes, although these cells may be also found in Sjögren's patients as well.[101]

Eyelid morphology changes in chronic oGVHD include subtarsal fibrosis and increased eyelid laxity. This was associated with decreased tear production and increased ocular dryness symptoms.[102] Kheirkhah et al found that varying amounts of subtarsal fibrosis were noted in over 50% of patients studied with oGVHD.[91] Meibomian gland atrophy, including hyperkeratinization of ductal orifices is a known complication of oGVHD. Necessary for the stability of the tear film, meibomian gland dysfunction is a significant issue for these patients and adjunct lacrimal gland destruction further worsens the surface disease. Meibomian gland morphology and function was shown to be worse on oGVHD patients than those with Sjogren's or other dry eye situations.[103]

Meibography can determine the status of the meibomian glands in chronic oGVHD and may help determine the stage (Figure 3). Hwang, et al found that infrared meibography showed rapid and aggressive meibomian gland destruction in select patients with oGVHD.[104] Interestingly, meibomian gland atrophy is significantly increased in oGVHD patients before HCT.[105] This suggests the inflammatory process that leads to ocular surface disease begins before transplant and likely related to either primary disease or chemotherapy or irradiation. These findings limit whether meibography is a predictor of oGVHD. The clinical association between the presence of conjunctival subepithelial fibrosis and ICCGVHD criteria was evaluated with only a mild correlation, and meibomian gland atrophy was not correlated to conjunctival scarring in a small study by Kusne, et al.[92] Further studies regarding clinical correlations are needed.

FIG. 3 Meibomography showing shortening and loss of the meibomian glands.

Tear fluid analysis for biomarkers may become useful in the diagnosis of chronic oGVHD, particularly proinflammatory cytokines. Riemens, et al reported that the cytokines interleukin-6 (IL-6) and interferon-γ (IFN-γ) were significantly elevated in patients with oGVHD.[20] IFN-γ was found to positively correlate with a decrease in Schirmer's tear production and tear break-up time (TBUT), but not OSDI score or symptoms. This suggests that IFN-γ may play a role in the early stages of oGVHD. IL-6 though was found to correlate with an increase in dry eye disease symptoms, vital staining and the OSDI score, indicating a role in the later stages. Tear levels of an interferon-inducible protein (IP-10/CXCL10) and interleukin-8/CXCL8 were found to be useful in predicting ocular surface inflammation at a sensitivity near 87% and specificity of about 95%.[18] Interestingly, tear cytokines, evaluated pre-stem cell transplant, may provide clues to susceptibility to oGVHD following transplant.[106]

DIAGNOSIS OF CHRONIC oGVHD

There are typically no unique features that are diagnostic for chronic oGVHD and many patients show a spectrum of clinical findings seen in ocular surface disorders. Likewise, the clinical examination for oGVHD is similar for any suspected ocular surface disease condition and includes symptom assessment, an inspection of the ocular surface integrity with vital stains, evaluation of tear volume and stability, and meibomian gland scanning. Osmolarity testing and tear matrix metalloproteinase-9 (MMP-9) screening may also be useful adjuncts. Additionally, the medical history should include questions regarding preconditioning regimes, type and time of transplant, the onset of other GVHD signs, related or unrelated match donor, and medications used for the GVHD response.

A symptom questionnaire such as OSDI has been recommended to be used both for clinical qualification

and as a comparison standard for research.[11,107,108] OSDI, SPEED, and other questionnaires are easily implemented by the hematologist and ophthalmic practitioners alike, allowing for screening and possible earlier detection of chronic oGVHD. Saboo, et al reported that the ODSI significantly compares to the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) that is used to assess patients' perceptions of their visual function and the impact of eye disease on their quality of life.[107,109] The study also showed that the quality of life score compared to that of patients with Sjögren's syndrome and that the pain scores were equal to ocular chemical burns. Lastly, the only clinical finding that significantly correlated with the OSDI score was corneal fluorescein staining, reflecting the degree of epitheliopathy. The most common symptoms reported by Balaram, et al were foreign body sensation (89%), red eyes (68%) and intermittent blurry vision (58%).[110] These symptoms are likened to other ocular surface disorders.

Pathak, et al found that no single diagnostic test or questionnaire is sufficient for the diagnosis of ocular graft versus host disease.[40] Ocular evaluation and significant test findings, along with a diagnosis of systemic GVHD, are best utilized for proper diagnosis according to ICCGVH criteria.[57] Clinical classification of oGVHD was recently reviewed in a large study of 148 oGVHD patients by Qiu, et al.[13] They noted the classic acute form had symptoms of dry eye with varying levels of conjunctival involvement, but minimal signs of corneal decompensation. Increased mucous secretion, conjunctival injection, and lacrimation were characteristic. Chronic oGVHD patients had severe dryness symptoms, including increased fibrous secretion, photophobia and reduced tear production. Chronic signs included corneal lesions, filamentary keratitis, corneal ulcers, and vascularization. Early oGVHD signs are often detected later, leading to delayed diagnosis and treatment. An example protocol using OSDI for early screening oGVHD is displayed in Figure 4.

Measurement by either Schirmer's or phenol red thread may show reduced tear volume if there is a deficient aqueous layer. Schirmer 1 scores have been reported to be less than 5 mm in 66% of patients upon the initial ophthalmic exam.[110] However, many oGVHD patients have significant reflex tearing from discomfort or poor tear clearance from cicatricial changes to either the eyelids or from stenosis of the lacrimal puncta, producing an overmeasurement of tear volume. This may result in underdiagnosis.

Additional testing such as MMP-9 (InflammaDry®) and confocal microscopy provides crucial information regarding early diagnosis and disease progression. Also, a recent prospective study by Giannaccare et al showed measurably different corneal biomechanical changes in corneal hysteresis and resistance factor as compared to controls.[81] They proposed that corneal stromal collagen fibril architecture changes due to oGVHD may lead to these biomechanical changes. Corneal hysteresis and resistance factor may be used as a possible indicator of disease severity and progression in the future.

FIG. 4 An example protocol using OSDI for early screening oGVHD.

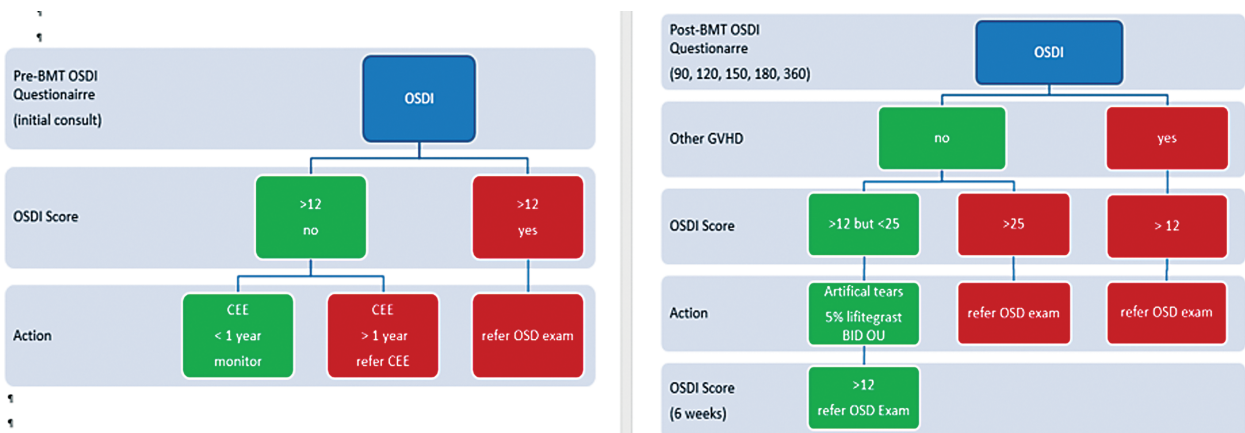


FIG. 5 Conjunctival changes including injection, adhesions, and subconjunctival fibrosis.

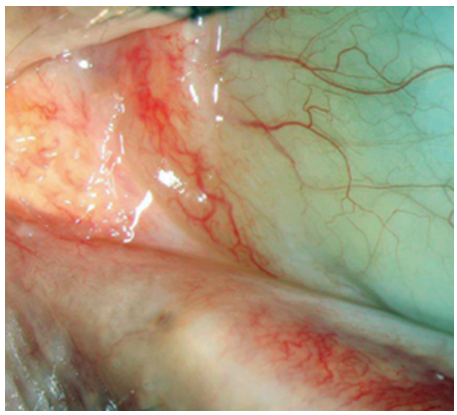
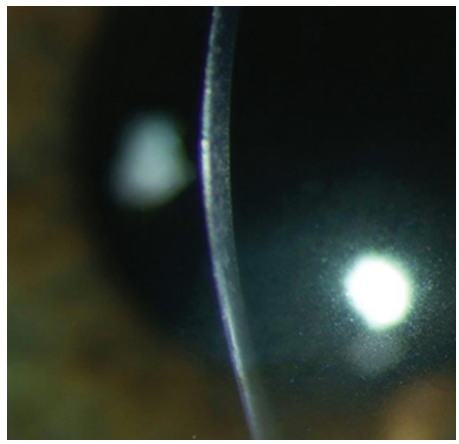


FIG. 6 Corneal scarring with thinning.



Careful biomicroscopy will reveal a thin tear meniscus and inspissated meibomian gland orifices. Reduced TBUT was shown to be less than 5 seconds in 71% of patients at presentation, with severe fluorescein staining (NEI score) in 58%.[110,111] There may be diffuse conjunctival chemosis or injection of both bulbar and palpebral surfaces. Chronic inflammation may lead to prominent conjunctivochalasis, which is highlighted with the use of lissamine green. Inspection of the palpebral conjunctiva may also reveal additional findings from papule formation to subepithelial fibrosis, particularly of the superior tarsus (Figure 5). In later stages, symblepharon or ankyloblepharon may develop.

Corneal findings include inferior punctate staining from incomplete blink or lagophthalmos. There may be persistent punctate epithelial erosions, hypertrophy and filaments in later stages. With prolonged cases, patients may develop decreased sensitivity or neurotrophic corneal changes, although the cornea may develop into a neurotrophic phase. One situation where this is likely to occur is post-herpetic corneal infection.[112] However, in most cases of oGVHD, corneal sensitivity is of limited value in initial diagnosis. Corneal ulceration, neovascularization, corneal thinning and perforation may be unfortunate morbidities in severe cases (Figure 6).

Anterior iritis is an uncommon finding in only 2–7% of patients, less likely as a presenting sign.[64,68,86,113,114] Posterior cataract formation can be rapid, although may be due to either pre-transplant chemotherapy, or concurrent post-transplant systemic and topical treatment with anti-inflammatory agents. Dilated posterior segment examination may reveal rare isolated retinal hemorrhages, papillitis or vascular occlusions, but again these are not diagnostic signs of oGVHD.[64]

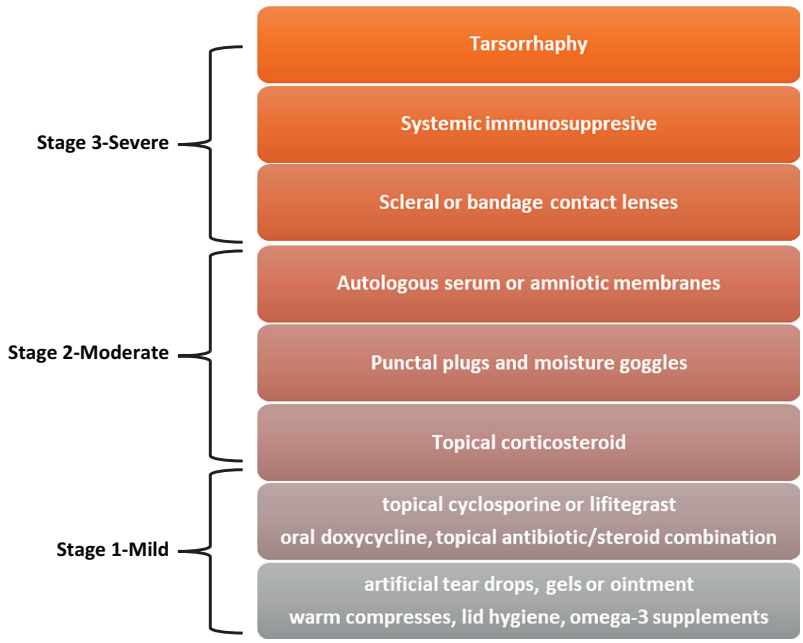
MANAGEMENT OF CHRONIC oGVHD

In general, screening and prevention of oGVHD is recommended for all transplant recipients. Flowers, et al, suggests ophthalmic examination at initial presentation of ocular symptoms and every 3–6 months thereafter or more frequently according to findings.[44] If there are no ocular manifestations with GVHD, then baseline at 100 days post-HCT and then yearly. Baseline screening before HCT with 100-day follow-up screening for early changes would be ideal.

Treatment for oGVHD starts typically with hematologist/oncologist practitioners when the patient first presents signs of ocular involvement. In oGVHD, a stepped treatment plan, summarized in Figure 7 should be used. This approach allows for better coordination between care team providers.[17,115–118]

Anecdotally, artificial lubricants and 0.05% cyclosporine-A (CsA) are usually the treatment of the first choice for hematologists/oncologists. A longitudinal, prospective, non-randomized small study of 20 transplant patients was pre-treated with CsA twice daily for 12 months after transplant. Only 1 out of 20 developed oGVHD during the 20 months follow -up period.[119] Further randomized large scale

FIG. 7 Stepped treatment of oGVHD.



study is needed regarding this promising oGVHD prophylaxis option.

Topical corticosteroids are the first-line therapy in moderate to severe stages of oGVHD but are not recommended in a non-ophthalmic setting as it is difficult to monitor for any ocular side effects.

Like all ocular surface issues, continuous lubrication to stabilize the tear film is a must. There have been limited studies with the use of artificial lubricants specifically with oGVHD and the broad reviews do not discuss specific type, frequency or duration. Patients must be educated to use the lubrication consistently and before symptoms emerge to attain the best effect. Preservative-free products are certainly preferred. Gel drops or ointments at night time may also be needed since cicatricial changes to the eyelids may cause lagophthalmos and exposure. The use of moisture goggles, environment humidification and avoidance of noxious stimuli are also conservative methods to control ocular evaporation.

Beyond the initial treatments, control of the ocular surface inflammation with a variety of agents have been used, including topical cyclosporine (CsA), lifitegrast and corticosteroids. These are usually given in addition to supportive measures for patients who have not responded. According to the Best Practice Guidelines of the American Academy of Ophthalmology, topical non-steroidal anti-inflammatory drugs should not be used in oGVHD due to the compromised corneal surface and anesthetic effect of these agents.[120]

The use of 0.05% CsA at BID dosing in chronic oGVHD has been well established and seems to be an effective treatment in mild to moderate stages.[121–123] Malta, et al, in a retrospective study, suggested the use of topical CsA before BMT may reduce the inflammatory response of the lacrimal gland post-BMT.[124] Berchicci et al also noted treatment effectivity with CsA use in a prospective study of 269 patients, with fewer relapses compared to topical steroids at 12 and 24 months follow up.[79] Many patients, particularly those with marked corneal epitheliopathy may not be able to tolerate the associated stinging and discomfort known to be side effects of topical CsA. In one study by Sanz-Marco, et al, nearly 50% of patients were intolerant.[125] The ocular discomfort may be mitigated by either placing the CsA in the refrigerator to provide a cooling effect upon installation or using reduced initial dosing of either QD or QOD. In cases recalcitrant with BID dosing, increasing to QID has shown to improve ocular surface staining in severe dry

eye.[126] Compounded 0.1 to 0.15% CsA has also been suggested to be an alternative treatment approach.[127] A new formulation of 0.09% CsA that uses a unique nanomicelles delivery system has demonstrated to increase tear production in keratitis sicca.[128] Care must also be used in oGVHD patients when prescribing CsA as many are susceptible to herpes viruses. When CsA is prescribed, patients may also need to be on prophylactic systemic antiviral therapy.

Lifitegrast may show improved effectiveness over CsA in chronic oGVHD since the mode of action involves blocking the interaction between ICAM-1 and LFA-1, reducing the recruitment of alloreactive T cells to the target organs.[129–132] While there have been no large scale prospective studies, Chhabra and others showed improved NIH severity symptoms scores in oGVHD with the use of 5% lifitegrast BID.[133] In this small retrospective case study series, approximately half (46%) of the patients had an improvement and none of the other patients had an increase in symptoms while on the lifitegrast. The majority of the patients (87%) had been on and failed artificial tears and topical cyclosporine.

When patients present with moderate to severe inflammation of the ocular surface, then the use of topical corticosteroids is indicated.[9,14,65,87,134] Robison, et al, showed a reduction in conjunctival hyperemia and control of cicatricial fibrosis with the use of 1% prednisolone acetate.[135] The time interval of the use was 7–13 weeks. Prolonged use of a corticosteroid is often needed to mitigate the inflammatory response but does increase the risk of elevated IOP and the development of posterior subcapsular cataracts. Careful monitoring in patients with corneal defects is critical to detect early secondary infections. “Soft” topical corticosteroids such as fluoromethalone and loteprednol have been suggested as alternatives to reduce the side effects, however; there have been no studies showing their effectiveness in oGVHD. Difluprednate has not been used typically except when there are contraindications to other treatments. Compounded 0.5% methylprednisolone solution has been used as an effective treatment when the desired response has not been achieved with 1% prednisolone.[136] A strategy to prevent reoccurrence of the oGVHD response is to overlap the corticosteroid with another agent such as cyclosporine or lifitegrast. This may help to prevent rebound as the steroid drop is withdrawn.

Tacrolimus, an interleukin-2 inhibitor, has also been used to address the inflammatory response from oGVHD. It can be used in either a 0.03–0.10% ointment or compounded drop. It may also be used as maintenance therapy after topical corticosteroids have been withdrawn.[137] Abud and associates showed that 0.05% topical tacrolimus was as effective as 0.5% methylprednisolone in lessening subjective complaints and reducing corneal fluorescein staining.[136]

Management of posterior blepharitis is essential to address meibomian gland dysfunction. Eyelid warming masks should be applied frequently along with lid hygiene and digital removal of lid margin debris and biofilm. Using oral doxycycline 50–100 mg twice a day is common practice but has not been demonstrated by clinical trials as to effectiveness. Although potentially useful in refractory meibomian gland disease, thermopulsation, intense pulse light, or ductal probing have not been reported to be used in oGVHD patients and the benefits of these emerging treatments remain unknown.

Despite the ongoing concern for potentially increasing contact time with inflammatory cytokines in tears, punctal occlusion or cautery can be helpful in patients with chronic oGVHD.[138] Sabti and colleagues found with patients that were followed for up to a year, a significant increase in patient comfort and a decrease in corneal fluorescein staining with silicon plug occlusion.[138] There may also be an added benefit of maintaining therapeutics on the ocular surface as well. Cautery is less desirable because of the potential for abnormal fibrosis and scarring of the eyelids.

Filamentary keratitis is one of the most difficult signs to manage. Topical corticosteroids and other agents including 5–10 % acetylcysteine may be needed long-term to control filament development. Filaments may develop due to the fibrosis of the lid and increased mechanical friction with the ocular surface, much like that seen in scleroderma.[91,92,139] Consistent lubrication is important to reduce these effects and oil-based artificial lubricants are preferred. A soft hydrophilic bandage contact lens can provide temporary relief and protection in these cases.[19]

Blood derived therapies such as autologous serum (AS), fresh frozen plasma, human albumin and platelet-rich in growth factor (PRGF) eye drops have shown effectiveness in reducing the discomfort and ocular signs associated with ocular surface conditions, including GVHD.[140–146] These agents are not typically used as first-line therapies but are reserved for patients that have a recalcitrant disease, such as persistent epithelial defects. They typically are compounded, are non-preserved and are generally not covered by insurance, all reasons which limit access to many patients.

AS drops are most commonly available in concentrations from 20–100%, depending on the severity of the condition. Patients can use the serum every one to four hours. They are used in combination with other therapies, including scleral contact lenses. Complication concerns are minimal, but contamination and the rare possibility of immune complex deposition in the cornea need to be monitored. AS drops have multiple benefits including biomechanical and biochemistry aspects.[147,148] It is the closest natural tear supplement available for lubrication and hydration. It has similar pH level and osmolarity, and contains increased concentrations of albumin, epithelial growth factor, transforming growth factor ß, vitamin A, lysozyme, surface IgA, fibronectin and other anti-inflammatory cytokines. Amniotic membrane eye drops have also been suggested as a treatment of severe keratitis sicca.[149]

Scleral contact lenses have also been found to be beneficial in the management of chronic oGVHD. Providing a protective barrier with the additional continuous bathing of the corneal surface has helped to reduced ocular pain and preserve the corneal integrity (150–153). There are many commercially available lenses including the BostonSight ®PROSE, Visionary Optics Jupiter Scleral™, EyePrintPRO™, and Alden Optical Zenlens™. Temporary bandage contact lenses have also been used to treat persistent corneal defects resistant to other topical therapies.[19,154] They are usually combined with a daily topical antibiotic for prophylaxis. Care must be given to periodic examination and compliance to avoid ocular infection or corneal ulceration. Inamoto, et al, showed that after two weeks of therapy using Bausch & Lomb PureVsion as a bandage lens, 58% of patients showed improvement in corneal punctate erosions.[19]

Amniotic membranes (AM), either cryopreserved or dehydrated, have been used as salvage therapy to heal persistent epithelial defects in many corneal conditions.[155–161] An amniotic membrane acts as physical barrier that protects the epithelium as it heals, reduces pain, and has anti-inflammatory substances that promote epithelial growth and repair. One caution with cryopreserved AM is it increases the risk of disease transmission in susceptible immunocompromised patients. Dehydrated AM, however; may have less of an effect from partial denaturization of proteins during the preparation process. There have been limited reports on the effectiveness of AM with recalcitrant oGVHD. Peric, et al did report a small case series indicating that their use may be beneficial.[156] In extreme cases, where AM have failed, salvage corneal transplant may be necessary if corneal perforation occurs.[162]

In concert with hematology oncologists, concurrent systemic therapy may help address the ocular complications. As the overall systemic response is managed, the ocular tissues may show improvement as well in the early presentation stages. Careful monitoring and treatment alterations should be tailored to the response. However; systemic therapies are less likely to be successful when there has been cicatricial scarring of the conjunctiva and eyelids. These situations are persistent and require more advanced interventions such as tarsorrhaphy.

CURRENT CLINICAL RESEARCH

While previous recent clinical trials have proven beneficial, further studies are ongoing to help provide crucial novel options for ocular graft-versus-host patients. Current treatment strategies have improved outcomes, yet there is still much to be learned.

A recently completed phase I/II study of a randomized placebo-controlled, double-blind, single centre design, examined the tolerability and preliminary efficacy of immunoglobulin eye drops in patients with dry eye disease. Efficacy was determined by OSDI patient rating scale improvement and corneal staining.[163]

To address the challenges surrounding the use of AS and platelet enriched plasma tears including the

non-uniformity of preparation, the unknown shelf life of the preparations, the use of non-preserved multi-dose packaging and the practical storage concerns, a proprietary standardized method for manufacturing is currently being studied.[164] A randomized, multicenter, double-masked placebo-controlled parallel phase I/II study to determine the safety and exploratory efficacy of topical fibrinogen depleted human platelet lysate in patients with dry eye secondary to GVHD is also in progress.[164]

Another ongoing study involves evaluating the tolerability and preliminary efficacy of recombinant human deoxyribonuclease (rhDNase) eye drops in patients with ocular GVHD. This study is a phase I/II randomized placebo-controlled double-blind single-center study.[165]

Also, a small multicenter, double-masked randomized placebo-controlled phase II trial of Thymosin B4 as a novel therapy showed significantly improved signs and symptoms of severe dry eye (including GVHD) while maintaining a good safety profile and significant improvement in signs and symptoms.[166]

Another study is looking at the safety and benefits of topical processed amniotic fluid drops. A randomized, double-blinded, placebo-controlled phase II study is currently underway. The response is measured via a composite of the NIH Consensus Conference for assessment in chronic GVHD and the International Dry Eye Workshop (DEWS) score. Visual acuity and corneal surface disease are also being measured.[167]

Pro-ocular™ 1% topical gel hopes to decrease or alleviate the signs and symptoms of GVHD after stem cell transplantation, is currently enrolling patients to look at efficacy and safety. This could hopefully reduce long-term drop instillation and improve quality of life. The gel is applied to the forehead twice daily. Glia OSD and NIH symptom questionnaires, corneal, conjunctival and eyelid changes will be observed.[168]

Another topical drop therapy, brimonidine tartrate nanoemulsion drops are being studied in patients with ocular GVHD. Currently, in phase 3 recruiting, this randomized, placebo-controlled, large multicenter study will evaluate the safety and efficacy of the medication versus placebo. The projected enrollment is 60 patients, much larger than many other studies. Outcomes rate redness and symptoms over the 12- week treatment. Ocular surface characteristics and tear secretion levels are also graded.[169]

Interestingly, the pathophysiology of mechanical stress in ocular surface disorders is being studied to target potential causes and hopefully provide insight into future treatment. The expression levels of diadenosine polyphosphates and mucin levels in mechanical stress-related ocular surface disorders are being investigated before and after treatment with a bandage contact lens (to reduce shearing stress). Tear samples and questionnaires will be evaluated.[170]

Systemic research may also prove beneficial for ocular GVHD as adjunctive therapies. Currently, randomized open-label multicenter phase 3 clinical trials are studying ruxolitinib versus best available therapy for corticosteroid refractory GVHD after allogenic stem cell transplantation. (REACH 3). This could also help manage ocular sequalae concurrently.[57]

Animal Studies

Regulatory T cells show promising results in preventing GVHD in a mouse model, following treatment of BMT patients with Interleukin-10 donor T cells.[171] Also, rebamipide, a mucin secretagogue, showed improved keratopathy and tear film in a mouse model of oGVHD.[172]

A mouse model and limited human study examined whether a SNARE protein vesicle-associated membrane protein 8 (VAMP8) was associated with the development of chronic oGVHD. The expression of VAMP8 in the chronic GVHD affected population was decreased, causing decreased tear secretion changes. Therefore, utilizing anti-VAMP8 as a potential treatment modality may allow future pathways for increased tear production.[173]

CONCLUSION

cGVHD is a major cause of mobility and mortality after HCT. As survival rates after transplant are improving, the incidence of oGVHD is increasing. Ocular manifestations are common and must be addressed early to reduce the chance of cicatricial changes to the ocular surface, particularly the lacrimal gland and conjunctiva. These complications can lead to decreased vision and substantially impact daily activities and quality of life. Often the symptoms

are noted along with other systemic findings of cGVHD and the continued development of accurate screening tools is essential to screen for early ocular symptoms. Recognition of dry eye symptoms and inflammation by the hematology/oncology team with the use of screening tools such as OSDI and InflammaDry™ may allow for earlier diagnosis and treatment. A stepped therapeutic approach by an eye care provider familiar with diagnosis and treatment of oGVHD should be used in conjunction with the hematology/oncology providers depending on the stage of the ocular findings. Many novel agents are being developed both for systemic complications as well as for oGVHD. Janus kinase inhibitors, Bruton's kinase inhibitors and Rho kinase inhibitors may be key future treatment options.

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