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# Use of Fluid-Ventilated, Gas-Permeable Scleral Lens for Management of Severe Keratoconjunctivitis Sicca Secondary to Chronic Graft-versus-Host Disease

*Kikuchi Takahide,[1] Pablo M. Parker,[2] Michael Wu,[3] William Y.K. Hwang,[4] Paul A. Carpenter,[1,3] Carina Moravec,[1] Barbara Stehr,[2] Paul J. Martin,[1,3] Perry Rosenthal,[5] Stephen J. Forman,[2] Mary E.D. Flowers[1,3]*

[1]Fred Hutchinson Cancer Research Center, [2]Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, [3]University of Washington, Seattle, Washington; [4]Singapore General Hospital, SingHealth, Singapore; and [5]Harvard Medical School and Boston Foundation for Sight, Boston, Massachusetts

Correspondence and reprint requests: Mary E.D. Flowers, MD, Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, D5-290, Seattle, WA 98109 (e-mail: mflowers@fhcrc.org).

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## ABSTRACT

**Keratoconjunctivitis sicca (KCS) occurs in 40%-60% of patients with chronic graft-versus-host-disease (cGVHD) after allogeneic hematopoietic cell transplantation. Although immunosuppressive therapy is the primary treatment of chronic GVHD, ocular symptoms require measures to improve ocular lubrication, decrease inflammation, and maintain mucosal integrity. The liquid corneal bandage provided by a fluid-ventilated, gas-permeable scleral lens (SL) has been effective in mitigating symptoms and resurfacing corneal erosions in patients with KCS related to causes other than cGVHD. We report outcomes in 9 consecutive patients referred for SL fitting for cGVHD-related severe KCS that was refractory to standard treatments. All patients reported improvement of ocular symptoms and reduced the use of topical lubricants after SL fitting resulting from decreased evaporation. No serious adverse events or infections attributable to the SL occurred. The median Ocular Surface Disease Index improved from 81 (75-100) to 21 (6-52) within 2 weeks after SL fitting, and was 12 (2-53) at the time of last contact, 1-23 months (median, 8.0) after SL fitting. Disability related to KCS resolved in 7 patients after SL fitting. The use of SL appears to be safe and effective in patients with severe cGVHD-related KCS refractory to conventional therapies.**


## KEY WORDS

Graft-versus-host disease • Keratoconjunctivitis sicca • Allogeneic hematopoietic cell transplantation

## INTRODUCTION

The term keratoconjunctivitis sicca (KCS) denotes inflammation caused by dryness of the conjunctiva and cornea. Ocular chronic graft-versus-host disease (cGVHD) can cause acute conjunctival inflammation, pseudomembranous and cicatricial conjunctivitis, and KCS. Dry eyes or KCS occurs in approximately 40%-60% of patients with cGVHD after allogeneic hematopoietic cell transplantation (HCT) [1-3] and may represent the only, or most significant, clinical manifestation and sequelae of cGVHD in some patients. Patients with KCS may develop corneal erosions and filaments causing severe pain and photophobia. If inadequately managed, corneal epitheliopathy can progress to persistent epithelial defects, sterile corneal ulcers, secondary infectious keratitis, and corneal perforation, leading to stromal scarring and loss of vision [4].

Systemic immunosuppressive therapy may be needed to halt inflammatory processes, and is sometimes indicated when cGVHD of the eye is resistant to local therapy or associated with other organ involvement [5]. cGVHD can cause irreversible damage to sebum and tear-producing cells, with sequelae resulting in considerable disability. For these patients, ancillary and supportive care for the eye is directed to improving ocular surface lubrication and decreasing inflammation. Such treatments include artificial tears,

long-acting ocular lubricants, punctal occlusion or cauterization, ophthalmic cyclosporine [6], topical corticosteroids, autologous serum eye drops [7], moisture chamber eyewear [8], and oral administration of cholinergic agents [2-5].

Supportive care for patients with severe cGVHD of the eye can improve the quality of life of afflicted individuals. The liquid corneal bandage provided by a fluid-ventilated, gas-permeable scleral lens (SL) has been effective in mitigating symptoms and resurfacing corneal erosions in the treatment of KCS because of other disorders [9,10]. We therefore analyzed our experience on the use of SL in individuals with cGVHD-related severe KCS refractory to other therapies. We report outcomes in 9 consecutive patients referred for SL fitting as treatment for cGVHD-related severe KCS that was refractory to standard therapies.

## PATIENTS AND METHODS

Between April 2004 and July 2006, 9 patients were fitted with SL for refractory KCS because of cGVHD following allogeneic HCT at the Fred Hutchinson Cancer Research Center or the City of Hope. A retrospective analysis was performed in November 2006 to describe the outcome of these 9 consecutive patients referred to the Boston Foundation for Sight, a nonprofit organization. In all cases, the decision to treat patients by fitting SL was prompted by debilitating ocular discomfort, visual impairment, or keratopathy despite systemic and local therapies as well as other supportive care. The status of cGVHD before lens placement was determined by patient interviews and a retrospective review of patient records. The involvement of other organs by cGVHD at any time before lens placement and at the time of lens placement was recorded, as was the duration of eye cGVHD prior to fitting the SL. Records were reviewed for prior topical therapy for dry eyes, including the use of artificial tears, cellulose ophthalmic inserts (Lacriserts), cyclosporine eye drops, doxycycline eye drops, punctal plugs, autologous serum tears, and moisture chamber eye wear. Data was also gathered regarding the use of systemic immunosuppressive treatments and cGVHD manifestations before and at the time of SL fitting and at the time of last contact.

Fitting of SL was performed by the Boston Foundation for Sight as previously described [9,10]. The SL, known as the Boston Scleral Lens, is lathed from a special polymer with an oxygen permeability value of $128 \times 10^{-11}$ $cm^2$ mL $O_2$/second mL mmHg and a center thickness ranging from 0.25 to 0.39 mm[8]. In customization, the curvature of the central back surface of each lens is designed to maintain shallow but definite clearance of the cornea and limbus after the lens settles, so that it is supported entirely by the sclera and not touching the cornea. The optimal lens vault and perimeter of the individual lenses are determined by on-eye evaluations of diagnostic lenses and other measurements.

**Table 1.** *Ocular Surface Disease Index© Questionnaire*

| |
|---|
| **Have you experienced any of the following during the last week?** |
| **1. Eyes that are sensitive to light?** |
| **2. Eyes that feel gritty?** |
| **3. Painful or sore eyes?** |
| **4. Blurred vision?** |
| **5. Poor vision?** |
| **Have problems with your eyes limited you in performing any of the following during the last week?** |
| **6. Reading?** |
| **7. Driving at night?** |
| **8. Working with a computer or bank machine (ATM)?** |
| **9. Watching TV?** |
| **Have your eyes felt uncomfortable in any of the following situations during the last week?** |
| **10. Windy conditions?** |
| **11. Places or areas with low humidity (very dry)?** |
| **12. Areas that are air conditioned?** |

Answers to questions are graded on a scale of 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; and 4, all of the time. The subtotal scores for answers 1 to 5 (A), answers 6 to 9 (B), and answers 10 to 12 (C) are added together (A + B + C) to obtain D (sum of scores for all questions answered). (E) is the total number of questions answered (excluding questions answered N/A).

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The response to the SL was assessed by use of the Ocular Surface Disease Index (OSDI). The OSDI is a 12-item questionnaire based on 3 subscales: vision-related function, ocular symptoms, and environmental triggers (Table 1). Answers to questions are graded on a scale of 0 to 4, where 0 indicates none of the time, 1 indicates some of the time, 2 indicates half of the time, 3 indicates most of the time, and 4 indicates all of the time. The OSDI has been validated as a reliable instrument used to assess severity of dry eye symptoms and vision-related function on a 0-100 scale, with higher scores correlating with increasing symptom severity and vision-related disability [11]. From a set of 12 questions (Table 1) administered, a score is calculated according to the formula: OSDI = [(sum of scores for all questions answered) $\times$ 25]/[total number of questions answered] [11]. From this score, the severity of ocular surface disease is derived according to a color scale, as depicted in Figure 1. In addition, questionnaires were administered retrospectively to inquire about symptoms and the use of artificial tears, punctal plug placement, use of moisture chamber eyewear, and disability because of eyes symptoms before and after SL placement and, at the time of last contact.

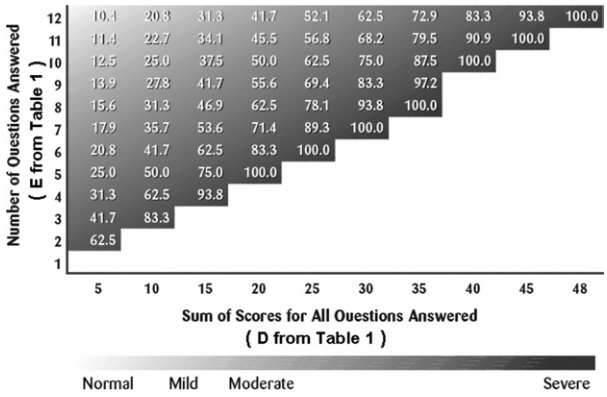


**Figure 1.** The OSDI scoring system. Using the sum of scores for all questions answered (D) and the number of questions answered (E), the corresponding score for the patient is then derived from the chart. The OSDI chart has a color scheme for computation of the severity of ocular surface disability. Reproduced with permission from Allergan®.

## RESULTS

Patient demographics are summarized in Table 2. Diagnoses at time of HCT were acute or chronic leukemia (n = 5), myelodysplastic syndrome (n = 2), aplastic anemia (n = 1) and multiple myeloma (n = 1). Median patient age at the time of SL fitting was 56 (range: 25-64) years. All patients had prior cGVHD involving multiple sites that required systematic immunosuppressive therapy including corticosteroids and cyclosporine. Four patients were receiving corticosteroids and 3 patients were receiving cyclosporine at the time of SL fitting. Two patients had also received treatment with azathioprine, 6 patients received mycophenolate mofetil, and 2 patients had been treated with PUVA therapy before SL fitting (Table 2). The most common cGVHD sites other than eyes at the time of SL fitting were 6 mucosal surfaces (oral and vagina), liver (n = 3), skin (n = 2), followed by gut (n = 1) and lungs (n = 1). At the time of SL fitting, 7 patients were receiving systemic immunosuppressive medications and 2 patients had discontinued administration of all systemic immunosuppressive medications after nonocular manifestations of cGVHD had resolved. Three patients had no active manifestation of cGVHD other than KCS at the time of SL fitting.

Table 3 presents patient-reported outcomes. The use of the SL led to improvement in ocular symptoms in all cases. No serious adverse events or infections attributable to the SL occurred. All 9 patients used topical lubricants frequently during the day before fitting the SL (baseline). In all patients, the frequency of topical lubricant use was reduced after SL fitting to twice daily or less (n = 3), 2 to 6 times daily (n = 4), or by a 50% reduction from baseline (n = 2). Prescription moisture chamber eye wear was needed in 3 patients before SL and no longer required in 2 of the patients at last contact. All 9 patients subjectively assessed themselves to have disability before fitting the SL, and 6 patients were no longer disabled after lens placement. One patient had significant difficulty inserting the SL, even with assistance (Patient 3).

The response to the SL was assessed by patient-reported ocular disability, use of ancillary eye care, and by use of the OSDI. As seen in Table 3, the median OSDI available improved from 81 (75-100) to 21 (6-52) within 2 weeks of SL fitting and was 12 (2-53) at the time of last contact, 1-23 months (median, 8.0) after SL fitting.

In Patient 1, SL fitting coincided with reinstitution of systemic immunosuppressive treatment, and cGVHD subsequently improved at other sites. Although the OSDI decreased promptly after SL fitting, systemic treatment could have contributed to the resolution of eye symptoms. Patient 2, who had healing of a persistent corneal epithelial defect after SL fitting (Figure 2), resumed therapy with prednisone and tacrolimus for management of other manifestations of cGVHD at 9 months after SL fitting. Patient 3 was the only patient among the 9 who had significant difficulty inserting the SL, even with assistance. This patient had significant initial improvement with regular use of the SL, but at present wears the SL only twice monthly for no more than 4 hours because mucous debris accumulates on the outside surface of the lens and interferes with vision during longer periods of use. Patients 4, 5 and 8 had significant improvement in ocular symptoms and also reported a significant reduction in the use of topical lubricants to once or twice daily after SL fitting. Patients 6 and 7 had debris collection on the lenses that has required removal and cleaning 1-2 times a day. Patient 9, despite improvement in ocular symptoms, remained disabled with impairment in his ability to read and drive at night.

## DISCUSSION

Our results document the response of chronic ocular GVHD-associated KCS to SL fitting. KCS is often accompanied by cGVHD activity in other organs, but may also represent the only manifestation of cGVHD [1]. The myriad and debilitating symptoms of KCS include burning, irritation, pain, foreign body sensation, blurred vision, and photophobia. Treatment measures that can control KCS or mitigate its symptoms are therefore important in restoring the quality of life of individuals after HCT.

Supportive care for the treatment of cGVHD of the eye has been recently summarized in the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease [4], and involves lubrication, con-

**Table 2.** *Patient Demographics*

| Characteristics | Cases | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Diagnosis | Aplastic Anemia | CML—CP | CML—BC | MDS/RA | CMML | CML—BC | CLL | MM | AML |
| Age at SL fitting (years) | 39 | 25 | 56 | 64 | 56 | 43 | 59 | 52 | 58 |
| Chronic GVHD | | | | | | | | | |
| Initial onset after HCT (months) | 3 | 7 | 7 | 12 | 7 | 26 | 12 | 2 | 6 |
| Involved organs other than eyes | Skin, liver, mouth, gut | Skin, liver, mouth | Skin, liver, mouth, vagina | Skin, liver, lung, gut, mouth | Skin, liver, lung | Skin, gut mouth | Mouth, joints, vagina | Skin, mouth | Skin, mouth |
| Total duration (months) | 208 | 20 | 38 | 110 | 156 | 46 | 42 | 69 | 36 |
| Total Duration of eye cGVHD (months) | 206 | 20 | 34 | 110 | 155 | 28 | 42 | 69 | 36 |
| Duration of eye cGVHD before SL fitting (months) | 192 | 7 | 10 | 92 | 147 | 25 | 36 | 63 | 36 |
| Involved Organs at time of SL fitting | Liver, mouth, GI tract | None | Skin, liver, mouth, vagina | None | None | Skin, eyes | Mouth, eyes | Mouth, eyes | Eyes, lungs |
| Prior Therapies for cGVHD | PDN, CSP, TAC, PUVA, AZA | PDN, CSP, TAC, MMF | PDN, CSP, TAC, MMF | PDN, CSP, MMF | PDN, CSP, TAC, AZA, PUVA | PDN, CSP, MMF | PDN, CSP, MMF | PDN, CSP, TAC | PDN, CSP, MMF |
| Prior Topical therapy for dry eyes | | | | | | | | | |
| Artificial Tears (AT) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Slow release AT (Lacriserts) | No | Yes | Yes | No | No | No | No | No | No |
| Cyclosporine eye drops | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes |
| Corticosteroids | No | No | No | No | Yes | No | No | No | Yes |
| Punctal plugs | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Autologous serum tears | Yes | No | No | No | No | No | No | No | No |
| Moisture chamber eye wear | Yes | No | Yes | Yes | No | No | No | No | No |
| Systemic immunosuppressive treatment at time of SL fitting | PDN, TAC | None | PDN, MMF | None | PDN | PDN, CSP, MMF, RAPA | CSP | TAC | CSP, MMF |

CML indicates chronic myelogenous leukemia; CP, chronic phase; BC, blast crisis; MDS, myelodysplastic syndrome; RA, refractory anemia; CMML, chronic myelomonocytic leukemia; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; AML, acute myelogenous leukemia; SL, scleral lens; PDN, prednisolone; CSP, cyclosporine; TAC, tacrolimus; AZA, azathioprine; MMF, mycophenolate mofetil; cGVHD, chronic graft-versus-host disease; GI, gastrointestinal.

**Table 3.** *Ocular Response to Scleral Lens (SL) Fitting*

| Characteristics | Cases | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Ocular Surface Disease Index* | | | | | | | | | |
| Before fitting SL | 100 | 88 | 75 | 79 | 92 | 81 | 81 | 75 | 77 |
| First 2 weeks after fitting SL | 21 | 50 | 41 | 12 | 6 | 6 | 21 | 23 | 52 |
| At last contact | 8 | 25 | 53 | 12 | 4 | 6 | 21 | 2 | 52 |
| Use of prescription-type moisture chamber eye wear | | | | | | | | | |
| Before fitting SL | Yes | No | Yes | Yes | No | No | No | No | No |
| First 2 weeks after fitting SL | No | No | Yes | No | No | No | No | No | No |
| At last contact | No | No | Yes | No | No | No | No | No | No |
| Subjective assessment of disability | | | | | | | | | |
| Before fitting SL | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| First 2 weeks after fitting SL | No | No | Yes | No | Yes | No | No | No | Yes |
| At last contact | No | No | Yes | No | Yes | No | No | No | Yes |
| Systemic Immunosuppressive medications at last contact | None | PDN, TAC | Unchanged | None | Unchanged | Unchanged | Unchanged | Unchanged | Unchanged |
| Last contact after SL fitting (months) | 14 | 13 | 23 | 18 | 8 | 4 | 4 | 4 | 4 |

*Scoring system shown in Figure 1.

trol of evaporation, control of drainage, and decreasing ocular surface inflammation. Ocular lubrication in severe KCS may be achieved by the use of artificial tears, viscous ointment, muscarinic receptor agonists, and cellulose ophthalmic inserts. Measures to control evaporation include the use of moisture chamber eye wear, tarsorrhaphy, and the use of lid care and warm compresses to maximize output of the meibomian glands that produce the outer oil layer of the tear film. Punctal occlusion using silicone plugs or thermal cauterization may be necessary to minimize fluid loss through drainage. Ocular surface inflammation may be reduced during systemic immunosuppressive treatment, judicious use of topical steroids, cyclosporine eye drops, autologous serum eye drops, and, interestingly, the ingestion of flaxseed oil. In very severe cases, transplantation of autologous limbal epithelial cells may provide benefit [12]. The use of SL helps to control evaporation by acting as a gas-permeable protective covering for the cornea and conjunctivae. This protection against evaporation and the mechanical trauma of the eyelids allows corneal defects to regenerate in the presence of adequate gaseous perfusion.

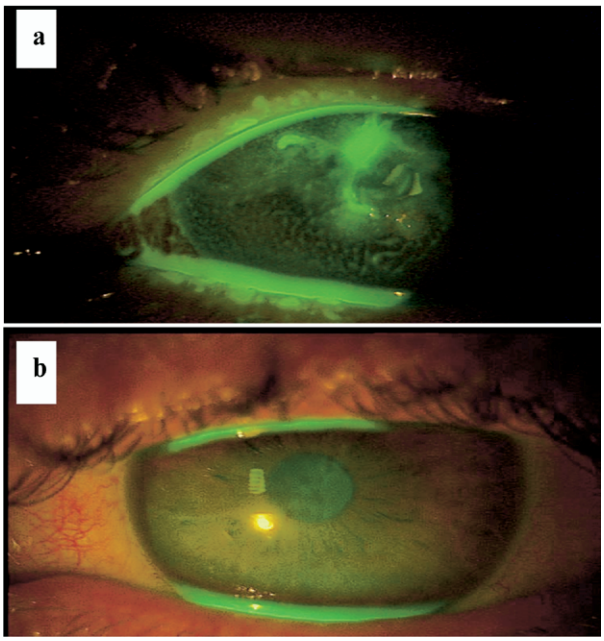


**Figure 2.** Scleral picture before and after SL insertion. Green fluorescein dye is used to delineate punctate keratopathy, corneal abrasions, and ulcerations. a, The cornea of patient 2 before initial lens insertion. The photograph shown in b was taken after wearing the lens for 6 hours and immediately after lens removal.

All patients fitted with SL for severe KCS because of cGVHD reported a significant reduction in topical lubricant use compared to baseline, most likely as a result of decreased evaporation and the protective therapeutic environment provided by the SL. Also remarkable was corneal healing noticed as early as 6 hours after SL placement in some of the cases. Both symptomatic and clinically visible improvement was seen in all patients.

Quantifiable indices, use of OSDI scores, a validated tool for patient self-reporting of dry eyes [8], also showed consistent improvement, although retrospective use of OSDI may limit the validity of this measure in our study. Nonetheless, patients can report accurately symptoms they experienced before SL wear, because they experience the same symptoms if they leave out the SL for several days. OSDI could be used in prospective studies of patients with KCS caused by cGVHD. In addition, a baseline assessment

of ocular surface disease, which was unavailable in our series, represents an objective measure of KCS severity that could be used in future prospective studies of ocular GVHD.

At the present time, fitting of the fluid-ventilated gas-permeable SL is available only at the Boston Foundation for Sight, a nonprofit organization. The process of custom-fitting this device is costly and time-consuming, making its use limited to patients who are severely disabled by eye symptoms that have not responded to other treatments. Furthermore, corneal endothelial dysfunction, if present, can provoke corneal edema. Hence, the use of the device is contraindicated in the presence of prior corneal edema and, in the absence of visible edema, an evaluation of response to temporary placement of a diagnostic gas-permeable SL is necessary. Also, some patients with considerable build up of eye debris may experience difficulty with extended use of the SL.

In this study, SL placement allowed for improvements in the quality of life and resumption of normal life activities in nearly all individuals suffering from debilitating cGVHD of the eye. We conclude that SL can be a safe and effective treatment for patients suffering from severe cGVHD-related KCS that is refractory to other therapies. Improved accessibility of SL device would be necessary to offer this therapy to more patients in need.

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