Diagnosis and Treatment of Ocular Chronic Graft-Versus-Host Disease: Report From the German–Austrian–Swiss Consensus Conference on Clinical Practice in Chronic GVHD

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Purpose: Ocular chronic graft-versus-host disease (cGVHD) is one of the most frequent long-term complications after hematopoietic stem cell transplantation and is often associated with significant morbidity and reduced quality of life.

Methods: The German/Austrian/Swiss Consensus Conference on Clinical Practice in cGVHD aimed to summarize the currently available evidence for diagnosis and (topical) treatment and to summarize different treatment modalities of ocular cGVHD. The presented consensus was based on a review of published evidence and a survey on the current clinical practice including transplant centers from Germany, Austria, and Switzerland.

Results: Ocular cGVHD often affects the lacrimal glands, the conjunctiva, the lids (including meibomian glands), and the cornea but can also involve other parts of the eye such as the sclera. Up to now, there have been no pathognomonic diagnostic features identified. The main therapeutic aim in the management of ocular cGVHD is the treatment of inflammation and dryness to relieve patients’ symptoms and to maintain ocular integrity and function. Therapy should be chosen in the context of the patient’s overall condition, systemic immunosuppressive therapy, symptoms, ocular surface integrity, and inflammatory activity. The consensus conference proposed new grading criteria and diagnostic recommendations for general monitoring of patients with graft-versus-host-disease for use in clinical practice.

Conclusion: The evidence levels for diagnosis and treatment of ocular cGVHD are low, and most of the treatment options are based on empirical knowledge. Topical immunosuppression, for example, with cyclosporine, represents a promising strategy to reduce inflammation and dryness in ocular cGVHD. Further clinical trials are necessary to elucidate risk factors for eye manifestation, complications, and visual loss and to evaluate staging criteria and diagnostic and therapeutic measures for ocular cGVHD.

Key Words: ocular graft-versus-host disease, chronic graft-versus-host disease, dry eye syndrome, consensus diagnosis and treatment, hematopoietic stem cell transplantation

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often accompanies cGVHD manifestations in other organs but can also be the only manifestation of cGVHD.\(^1,2\)

Ocular cGVHD can theoretically affect every layer of the eye. Although typically considered a disease of the lacrimal glands and the conjunctiva with keratoconjunctivitis sicca (KCS) as the most common manifestation,\(^3\) ocular cGVHD often affects the lids, the meibomian glands, and the cornea.\(^2\) In rare cases, cGVHD can also involve the sclera; manifestations in other parts of the eye such as anterior chamber, vitreous, and choroid have been rarely described in acute graft-versus-host disease (GVHD).\(^2,7\) However, special forms of GVHD with characteristics of both acute and cGVHD occurring simultaneously (eg, persistent, recurrent or late-onset acute GVHD, acute pattern cGVHD, and overlap forms) have been more frequently observed, which seems to apply also to ocular GVHD.\(^2,5\) Therefore, the traditional definitions of acute GVHD (occurring before day 100) and cGVHD (having onset after day 100) have been redefined.\(^1,5\)

The ocular surface disease in cGVHD is often irreversible and can be a cause of vision loss in severely affected patients. Primarily T-cell–related inflammatory processes, apoptosis, and fibrosis are currently thought to cause the dry eye and ocular surface disease in cGVHD.\(^6\) Recently, T\(_{17}\)-associated chemokines haven been identified in the conjunctiva of patients with ocular cGVHD.\(^7\) In other dry eye diseases (eg, Sjögren syndrome), the dryness itself maintains the chronic inflammatory processes of the ocular surface.\(^8\) Anti-inflammatory drugs such as topical steroids and cyclosporine eye drops have been shown to be effective in the therapy of cGVHD-related and non-cGVHD-related KCS.\(^8,15-17\) The main therapeutic aim in the management of ocular cGVHD is therefore the treatment of both inflammation and dryness to relieve patients’ symptoms and to maintain ocular integrity and function.

**MATERIALS AND METHODS**

The German/Austrian/Swiss Consensus Conference on Clinical Practice in Chronic GVHD aimed to summarize the currently available evidence for diagnosis and topical treatment of ocular cGVHD and to provide practical guidance for clinical use. The presented consensus was based on a review of published evidence and a survey on the current preferred clinical practice including transplant centers from Germany, Austria, and Switzerland. The literature search was performed by the working group on ocular cGVHD within the Consensus Conference using the PubMed database (January 1990 to July 2010). Thirty-one of 37 transplant centers performing allogeneic HSCT within Germany (n = 34), Austria (n = 3), and Switzerland (n = 1) responded to a paper-based survey sent via e-mail to the representatives of the centers. The survey was sent in June 2009 to the representatives of 37 transplant centers performing allogeneic HSCT to document the current practice before the consensus conference and to identify areas of disagreement between transplant centers. Moreover, the consensus was circulated among all transplant centers performing allogeneic HSCT in Germany, Austria, and Switzerland and was discussed during the Consensus Conference Meetings in Regensburg (November 2009) and Wiesbaden (May 2010). Overall, 58 German, Austrian, and Swiss transplant centers participated in the consensus conference representing 81% of all allogeneic HSCT centers. The Consensus Conference was organized under the auspices of the German working group on bone marrow and blood stem cell transplantation (DAG-KBT) and the German Society of Hematology and Oncology (DGHO), the Austrian Stem Cell Transplant Working Group of the Austrian Society of Hematology and Oncology, the Swiss Blood Stem Cell Transplantation (SBST) Group, and the German–Austrian Paediatric Working Group on Stem Cell Transplantation (Päd-Ag-KBT). In addition, the consensus manuscript was discussed and approved by an expert panel of the cornea working group of the German Ophthalmology Society (DOG).

The evaluation of evidence with the subsequent recommendation was graded according to the system used in grading of supportive care published by Couriel et al.\(^18\) The evidence of the majority of treatment options in ocular cGVHD is sparse, and therefore, for most of the therapeutic options, the strength of recommendation falls into category C. Where evidence from the use in cGVHD (hallmarked as “a”) was not available or insufficient, additional studies from the treatment of analogous diseases (“b”) were evaluated.

**RESULTS**

**Clinical Signs and Symptoms of Ocular cGVHD**

There are no specific symptoms or clinical signs (Table 1) of ocular cGVHD.\(^2\) Ocular cGVHD partially mimics other immunologically mediated inflammatory diseases of the ocular surface and can in some cases resemble acute GVHD manifestations as described above. Typical symptoms of cGVHD are dry eye, irritation, itchiness, grittiness, foreign body sensation, burning, epiphora (excessive tearing), photophobia, pain, redness (being also a subjective feature), and blurred vision. In rare cases, pain and redness can be related to scleritis. Visual impairment can also be due to the rare intraocular involvement of anterior chamber, vitreous, and choroid.

Quality of life is often significantly reduced because of the severe ocular discomfort that forces the patients to use very frequent application of lubricants (eg, up to every 5 minutes), interfering with everyday activities including reading, being outdoors, and working on a computer. In severely affected patients, the disease can lead to extensive vision loss or even blindness because of corneal or intraocular complications.

In pediatric patients, clinical features of ocular cGVHD are similar to adults,\(^19,20\) but children rarely report dry eye symptoms. Therefore, pediatric patients and their parents have to be asked specific questions regarding dry eye symptoms like pain, eye rubbing, or secretion. Sensitivity to light can be the predominant symptom of ocular cGVHD in children.

**Diagnostic Recommendations for Ocular cGVHD**

The presence of clinical signs such as conjunctivitis or lacrimal gland dysfunction may not always represent ocular
cGVHD because other conditions such as infectious diseases, side effects of medications, and conditioning treatments (eg, total body irradiation) can also present with similar clinical findings. It is important to set the ocular clinical findings into the context of the patient’s symptoms, other manifestations of cGVHD, systemic treatment, and clinical course.2

The patient’s medical history is essential because the new onset of severe refractory dry eye disease and a decrease in Schirmer scores in combination of worsening ocular symptoms is suggestive for diagnosis of ocular cGVHD.2

According to Filipovich5 and Kim et al,2 the diagnosis of ocular cGVHD requires a positive Schirmer test (without anesthesia) plus another distinctive feature (Table 2): Schirmer scores less than 5 mm plus 1 or more organ involvement or Schirmer scores 6–10 mm plus new onset of KCS (signs and symptoms).21 The consensus conference recommends in clinical practice the application of these distinctive features and diagnostic criteria that were primarily developed for clinical trials.5 However, sensitivity and prognostic values of ophthalmological diagnostic measures for ocular cGVHD have not been determined yet, for example, the Schirmer scores may vary depending on several factors and destruction of the meibomian glands as a manifestation of cGVHD may occur despite normal Schirmer scores. Wang et al22 recently published baseline features of HSCT recipients with or without GVHD-related dry eye. Further studies are necessary to evaluate the prognostic value of different ophthalmological tests for the assessment and follow-up of ocular GVHD in clinical practice.

**Ophthalmological Workup**

Complete ophthalmological examination including a visual acuity test, slit-lamp examination using vital dyes (eg,

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**TABLE 1. Clinical Manifestations of Ocular GVHD**

<table>
<thead>
<tr>
<th>Localization</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Pseudoptosis (Fig. 1), frequent blinking, constant squinting, photophobia, and decrease in visual acuity</td>
</tr>
<tr>
<td>Lacrimal glands</td>
<td>Cicatricial occlusion of the lacrimal puncta (Fig. 2)</td>
</tr>
<tr>
<td>Lacrimal duct</td>
<td>Meibomian gland obstruction (Fig. 1), anterior and posterior blepharitis (Fig. 1), erythema, edema, telangiectasias (Fig. 1), trichiasis, hyperkeratosis, cicatricial entropion, and periorbital hyperpigmentation (Fig. 1)</td>
</tr>
<tr>
<td>Lids</td>
<td>Conjunctival hyperemia (Fig. 1), hyperemia with chemosis and/or serosanguineous exudate, (pseudo)membranous conjunctivitis (Fig. 1), cicatricial changes of the palpebral conjunctiva (subtarsal fibrosis) (Fig. 2), conjunctival necrosis with reduced goblet cell density, and LIPCOF</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>Episcleritis, scleritis, posterior scleritis*</td>
</tr>
<tr>
<td>Sclera</td>
<td>Punctate keratopathy (Fig. 3), corneal sloughing (Fig. 3), filamentary keratitis (Fig. 3), superior limbic keratoconjunctivitis (persistent or recurrent), corneal erosion (Fig. 4), corneal thinning (Fig. 4), corneal ulcer, corneal scarring (Figs. 3, 4), corneal vascularization, corneal perforation, and corneal calcification</td>
</tr>
<tr>
<td>Anterior chamber</td>
<td>Anterior chamber cells</td>
</tr>
<tr>
<td>Vitreous</td>
<td>Vitreous cells</td>
</tr>
<tr>
<td>Choroids</td>
<td>Choroidal thickening* and serous detachment*</td>
</tr>
</tbody>
</table>

*Rarely seen, typically associated with acute GVHD.
LIPCOF: lid-parallel conjunctival folds.

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**TABLE 2. Diagnosis of Ocular cGVHD**

| Distinctive features seen in ocular cGVHD, insufficient alone to establish a diagnosis of cGVHD (according to Filipovich et al,1 Filipovich,5 Baird and Pavletic21) | New onset dry, gritty, painful eyes* |
| Other features can be seen as part of the cGVHD symptomatology if diagnosis is confirmed (according to Baird and Pavletic21) | Cicatricial conjunctivitis |
| Diagnostic criteria, sufficient for diagnosis of ocular cGVHD in patients who have GVHD involving at least one other organ (according to Kim and Dunn,2 Kim2) | KCS* |
| Diagnostic criteria for GVHD-related KCS (according to Couriel et al22+) | Confluent areas of punctate keratopathy |
| | Photophobia |
| | Periorbital hyperpigmentation |
| | Blepharitis (erythema of the eyelids with edema) |
| | Mean Schirmer score ≥ 5 mm (Schirmer test without anesthesia)† or New onset of keratokonjunctivitis sicca (signs and symptoms) with a Schirmer score of 6–10 mm |
| | Appropriate symptoms |
| | Tear production averaging ≥ 5 mm (Schirmer test)† |
| | Keratitis |

*Diagnosis of cGVHD requires biopsy or Schirmer test (≥5 mm).
†As Schirmer scores can be affected by several other factors, they must be considered in the context of the patient’s overall status.
‡Developed for clinical trials.
fluorescein, Lissamine green, bengal rose stain), thorough sub-tarsal inspection, tear film breakup time (BUT), Schirmer test (especially without anesthetic), is essential for patients with suspected cGVHD. Microbial (especially viral) swabs are useful to rule out microbial infections. However, infectious diseases of the ocular surface do not preclude diagnosis of ocular cGVHD. Special diagnostics such as osmolarity of the tear film, microscopy of a tear smear (fern test), meibomian gland diaphanoscopy, corneal sensitivity, in vivo confocal microscopy for inflammatory cells (eg, by HRT II/III with Rostock cornea module), photodocumentation, and so on, may be additionally performed where applicable and may be useful for therapeutic decisions and follow-up and in clinical studies.

Funduscopie is necessary to rule out GVHD involvement of the posterior segment of the eye and infectious diseases such as cytomegalovirus retinitis under immunosuppressive treatment. Slit-lamp examination of the lens should be performed to diagnose posterior subcapsular cataract, which is frequent in patients with systemic cGVHD secondary to steroid and/or radiation treatment. Assessment for glaucoma including measurement of the intraocular pressure and eventually visual field testing is indicated to detect secondary glaucoma because of systemic or topical steroid therapy.

The ophthalmological workup has to be adapted to the patient's overall condition and can be restricted to a minimum if necessary. In pediatric patients in particular, the examination should be as noninvasive as possible (eg, the Schirmer test should be avoided in children) and may be focused on indirect signs and symptoms of dry eye and ocular surface disease. However, slit-lamp examination and fluorescein staining are necessary to diagnose punctate keratopathy and complications such as corneal erosions or ulcers.

Evaluation of symptoms using quality-of-life questionnaires (eg, Ocular Surface Disease Index) can be helpful in addition to the National Institutes of Health (NIH) scoring system (see clinical grading of ocular GVHD) to track the course of disease and the response to treatment.

Concerning the recommendations for general monitoring of patients with cGVHD, Couriel et al proposed in the Ancillary Therapy and Supportive Care Working Group Report an ophthalmological evaluation (including the Schirmer test and assessment for glaucoma) every 3–12 months for 5 years after HSCT. Participants in the German/Austrian/Swiss Consensus Conference agreed in recommending for clinical practice: (1) a baseline ophthalmological workup including the Schirmer test before HSCT, and (2) a screening examination at day 100–200 after HSCT, and (3) an ophthalmological assessment in case of ocular symptoms or any other manifestation of GVHD (Table 3). These examinations should be performed by an ophthalmologist. The advantages of this screening protocol are (1) to provide a baseline examination to detect progressive KCS earlier, (2) to be able to diagnose ocular cGVHD earlier (eg, decrease in Schirmer scores, inflammation of the conjunctiva), and (3) to allow an early start with treatment to prevent excessive inflammation and scarring processes and sight-threatening complications and improve symptoms and quality of life. Additionally, putative risk factors may be identified. The recommendations for ocular monitoring have to be evaluated in the future.

### Histopathological Assessment

Histopathological features in conjunctival specimens of ocular cGVHD are lymphocytic infiltration, lymphocyte exocytosis, epithelial cell necrosis, satellitosis (single cell necrosis with surrounding lymphocytes), vacuolization of the basal epithelium and reduced goblet cell density, epithelial attenuation, and squamous metaplasia. In selected cases, conjunctival biopsy (snip biopsy from the inferotemporal bulbar conjunctiva according to Shulman et al and/or impression and brush cytology of the conjunctiva may be indicated (eg, in symptomatic patients with normal Schirmer score and no other documented cGVHD). Because of the diagnostic limitations of conjunctival biopsies, the consensus conference participants do not recommend biopsies routinely in every patient with cGVHD in clinical practice. However, further clinical studies including biopsies and cytology of the conjunctiva are necessary in the future to identify putative pathognomonic histological and immunohistochemical features of ocular cGVHD.

### Clinical Grading of Ocular cGVHD

The severity of the ocular surface disease depends on the involvement of the different ocular tissues (eg, lacrimal gland, conjunctiva, lids, and cornea) and the extent of tear film disturbance. If all 3 functionally important layers of the tear film (mucus layer, aqueous layer, and lipid layer) are defective, patients often have extreme dry eyes resulting in severe ocular surface disease and chronic inflammation: (1) Conjunctival necrosis and inflammation often lead to scarring and fibrosis (ie, cicatricial conjunctivitis, subtarsal fibrosis) and significantly decreased goblet cell density with disturbance of the mucus phase of the tear film; (2) lacrimal gland involvement with inflammation and fibrosis of the gland result in severe lacrimal gland dysfunction with reduction of the aqueous phase of the tear film and KCS; (3) blepharitis with meibomian gland dysfunction leads to a defective tear film lipid layer with tear film instability and increased evaporation, epithora, and chronic inflammation.

The grading criteria for conjunctival disease in ocular GVHD, which have been introduced by Jabs et al, are principally for patients with acute GVHD: conjunctival hyperemia (stage I), hyperemia with chemosis and/or serosanguineous exudates (stage II), pseudomembranous conjunctivitis (stage III), and pseudomembranous conjunctivitis with concomitant sloughing (stage IV). Pseudomembranous conjunctivitis can rarely occur in cGVHD and is partly considered as an acute variant of cGVHD. In 2004, Robinson et al introduced clinically relevant grading criteria to better assess the conjunctival involvement in cGVHD: grade 1 is defined as conjunctival hyperemia occurring on the bulbar or palpebral conjunctiva in at least 1 eyelid. Grade 2 has palpebral conjunctival fibrovascular changes occurring along the superior border of the upper eyelid or the lower border of the tarsal plate of the lower eyelid, with or without conjunctival epithelial sloughing, involving <25% of the total surface area in at least 1 eyelid. Grade 3 is defined as palpebral conjunctival fibrovascular changes occurring along the superior border of the upper eyelid or the lower border of the tarsal plate of the lower eyelid, involving 25%–75% of the total surface area in at least 1 eyelid. Grade 4 involves >75% of the...
Up to now, staging criteria have not represented the complete spectrum of disease. Novel approaches of clinical staging for better assessment of ocular cGVHD should be discussed and evaluated. The consensus conference participants agreed that they may include the overall extent of cGVHD with respect to the following:

1. Tissue involvement:
   a. The extent of lacrimal gland dysfunction
   b. The involvement of the lids (eg, blepharitis, meibomian gland dysfunction)
   c. The involvement of the conjunctiva (eg, cicatricial conjunctivitis)
   d. The corneal involvement (eg, keratitis, epithelial defects, and corneal ulceration)

2. Inflammatory activity (eg, hyperemia of the bulbar conjunctiva may be chronically present when ocular cGVHD is not well controlled)

3. The presence of complications and functional impairment (Table 4)

As proposed by the NIH consensus, the severity of cGVHD can be assessed by applying the ocular portion of the comprehensive organ scoring system: score 0, no symptoms; score 1, mild symptoms of dry eye or asymptomatic signs of KCS; score 2, moderate dry eye symptoms partially affecting activities of daily living, requiring drops >3 × per day or punctal plugs, without vision impairment; and score 3, severe dry eye symptoms significantly affecting activities of daily living or unable to work because of ocular symptoms or loss of vision caused by KCS.1

The consensus conference participants agreed that a more detailed and standardized documentation (exceeding Schirmer scores and symptoms) of ocular cGVHD involvement in staging forms for cGvHD therapy (www.gvhd.de) would be helpful.

**Therapeutic Management**

In general, therapeutic strategies should be based on an individually adapted and multidisciplinary therapy2,10,28 and should be performed in the context of the patient’s overall condition, systemic therapy, symptoms, and the inflammatory activity. An ophthalmologist who is knowledgeable about HSCT, GVHD, and systemic medications should be involved in coordination of care if possible.18

Topical treatment plays a major role in ocular cGVHD29 because (1) lubrication of the ocular surface cannot be sufficiently achieved by systemic treatment and requires topical lubricants, although systemic immunosuppressive therapies can lead to an overall improvement of ocular cGVHD2,30; (2) higher drug concentrations on the ocular surface can be achieved by topical drugs compared with systemic administration; and (3) topical immunosuppressive drugs (eg, corticosteroids or cyclosporine eye drops) may be continued as the only immunosuppressive

### Table 3. Consensus Conference Proposal for Diagnostic Measures for Assessment of Ocular GVHD

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline examination after conditioning treatment and before HSCT</td>
<td>Visual acuity test, slit-lamp examination including subtarsal inspection and fluorescein staining, Schirmer test, and funduscopic examination.</td>
</tr>
<tr>
<td>Baseline ophthalmological assessment at day 100–200</td>
<td>Visual acuity test, slit-lamp examination including subtarsal inspection and fluorescein staining, and Schirmer test.</td>
</tr>
<tr>
<td>Ophthalmological assessment if any other manifestation of GVHD or ocular symptoms</td>
<td>Visual acuity test, slit-lamp examination including subtarsal inspection, vital dyes, Schirmer test, additional tests if indicated (eg, tear film breakup time), tonometry, and funduscopic examination.</td>
</tr>
<tr>
<td>Routine ophthalmological assessment for 5 y after HSCT</td>
<td>Including Schirmer test and glaucoma and cataract assessment (according to Couriel et al19).</td>
</tr>
<tr>
<td>Conjunctival biopsy</td>
<td>Indicated in individual or uncertain cases (eg, ocular signs or symptoms with no other documented GVHD) or in clinical studies.</td>
</tr>
</tbody>
</table>

Diagnostic measures should be adapted to the patient’s overall condition and age; for example, in general, the Schirmer test should not be performed in children.

### Table 4. Conference Proposal for Staging and Documentation Criteria for Ocular cGVHD

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involvement of different ocular tissues</td>
<td>a. Extent of lacrimal gland dysfunction (including Schirmer test results)</td>
</tr>
<tr>
<td></td>
<td>b. Involvement of the lids (eg, blepharitis, meibomian gland dysfunction, and erythema)</td>
</tr>
<tr>
<td></td>
<td>c. Involvement of the conjunctiva (eg, cicatricial conjunctivitis)</td>
</tr>
<tr>
<td></td>
<td>d. Involvement of the cornea (eg, keratitis and epithelial defects)</td>
</tr>
<tr>
<td></td>
<td>e. Others (eg, scleritis)</td>
</tr>
<tr>
<td>Inflammatory activity (eg, redness of the lid margins, hyperemia of the conjunctiva)</td>
<td>a. No inflammation</td>
</tr>
<tr>
<td></td>
<td>b. Mild inflammation</td>
</tr>
<tr>
<td></td>
<td>c. Moderate inflammation</td>
</tr>
<tr>
<td></td>
<td>d. Severe inflammation</td>
</tr>
<tr>
<td>Presence of sight-threatening complications/functional impairment</td>
<td>a. Complications: for example, corneal perforation</td>
</tr>
<tr>
<td></td>
<td>b. Functional impairment: e.g. reduced visual acuity</td>
</tr>
<tr>
<td></td>
<td>c. Secondary glaucoma</td>
</tr>
</tbody>
</table>
treatment in ocular cGVHD and allow tapering and cessation of systemic immunosuppression.

Preservative-containing eye drops are cytotoxic for ocular surface epithilia (including conjunctival goblet cells) and should be avoided (especially if application is required more than 4 times per day). Phosphate-containing eye drops can promote corneal calcifications especially in cases of corneal epithelial defects (corneal erosions or ulcers), and patients with ocular cGVHD seem to be at risk for this complication.32 Besides topical and systemic drug treatments and supportive care, the control of environmental factors is helpful (e.g., occlusive eye wear, humidified environment, and sufficient intake of fluids). In case of antiglaucomatous treatment, topical prostaglandin equivalents should be avoided if possible because of their proinflammatory potential. Concerning pediatric patients, experience is limited and dosage recommendations for topical and systemic medications have not been evaluated yet. However, early and sufficient topical treatment is warranted especially in children because of the need of sparing systemic corticosteroids. There are 8 main therapeutic principles/treatment options for ocular cGVHD (Table 5).

**Decreasing Ocular Surface Inflammation**

**Topical Cyclosporine**

The use of topical cyclosporine eye drops is appropriate because ocular cGVHD is mediated by T cells, and cyclosporine acts specifically to suppress T cells. Cyclosporine eye drops have been shown to be effective in the treatment of dry eye diseases of various causes including ocular cGVHD.8,11–14 The main therapeutic aim of cyclosporine eye drops is a reduction of inflammation, apoptosis, and subsequently dryness, resulting in a relief of symptoms and a reduced need for lubricants. In randomized clinical trials, cyclosporine eye drops have been shown to improve the Schirmer test and the tear film breakup time, to increase the number of conjunctival goblet cells, and to reduce punctate keratopathy in patients with KCS.8,11,12 Therefore, cyclosporine eye drops are not only indicated in patients with inflammatory activity of ocular cGVHD but also in patients with dry eye without visible inflammatory activity (but underlying inflammatory processes).9

To date, the recommended dosage of cyclosporine eye drops in cGVHD is 0.05% twice daily as long-term treatment. Recently, a more frequent application (3–4 times per day) has been described in refractory patients.10 Cyclosporine eye drops are available in Europe as a pharmacy-compounded oily formula and in the United States as Restasis (Allergan, Irvine, CA) eye drops. Patients should be informed about the possible side effects as burning, stinging, and redness (which seem to occur more frequently with the oily formula) and about the delayed therapeutic effect because improvement is not expected until several weeks after the start of therapy. Tolerance can be improved in some patients by prior application of lubricants. In the survey among German, Austrian, and Swiss transplant centers, cyclosporine eye drops are frequently applied by 9 of 31 responding centers, another 4 use them occasionally, and 7 infrequently.

Subconjunctival cyclosporine implants are under evaluation in a National Eye Institute, randomized, phase I, clinical trial for treatment of KCS associated with cGVHD (05-EI-0002) and may be a therapeutic option in the future.17 Furthermore,

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**TABLE 5. Treatment Modalities for Ocular cGVHD (Including Evidence and Recommendation Levels as Shown in Tables 6 and 7)**

<table>
<thead>
<tr>
<th>Anti-inflammatory therapy</th>
<th>Topical steroids (C III-I), topical cyclosporine (C III-I), and systemic immunosuppressive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubrication</td>
<td>Preservative-free artificial tears or gels (A 1 b), ointment at bedtime, viscous tears/gels during daytime (B 1 b), and systemic therapy: cemeline and pilocarpine (C I b)</td>
</tr>
<tr>
<td>Autologous serum eye drops</td>
<td>C I b/C III-I</td>
</tr>
<tr>
<td>Control of evaporation</td>
<td>Treatment of blepharitis: warm compresses, lid hygiene (B II b), topical anti-inflammatory therapy with calcineurin inhibitors (C II b), systemic therapy with doxycycline/tetracycline (C III-I), and partial tarsorrhaphy (C II b)</td>
</tr>
<tr>
<td>Control of drainage</td>
<td>Punctal plugs and punctal occlusion (B 1 b/C III-I)</td>
</tr>
<tr>
<td>Scleral lenses</td>
<td>C II a</td>
</tr>
<tr>
<td>Prevention of infectious diseases</td>
<td>Prophylactic topical antibiotic treatment in cases of epithelial erosions/ulcers or use of bandage contact lenses, prophylactic antiviruses treatment if indicated (C III)</td>
</tr>
<tr>
<td>Management of complications</td>
<td>Epithelial debridement, bandage contact lenses, temporary amniotic membrane bio-onlays, amniotic membrane transplantation, lid surgery, tarsorrhaphy (C III-I), and limbal stem cell transplantation and keratoplasty (C III-3)</td>
</tr>
</tbody>
</table>

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**TABLE 6. Strength of Recommendation (According to Couriel et al18)**

<table>
<thead>
<tr>
<th>Strength of Recommendation Level</th>
<th>Definition of Recommendation Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Should always be offered.</td>
</tr>
<tr>
<td>B</td>
<td>Should generally be offered.</td>
</tr>
<tr>
<td>C</td>
<td>Evidence for efficacy is insufficient to support for or against or evidence might not outweigh adverse consequences or cost of the approach. Optional.</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.</td>
</tr>
</tbody>
</table>
cyclosporine 0.05% is currently being evaluated in a randomized, placebo-controlled, phase III trial (NCT00755040) for primary prevention of cGVHD after allogeneic HSCT. Cyclosporine eye drops and other calcineurin inhibitors such as pimecrolimus and tacrolimus are effective in the treatment of blepharitis, which also frequently occurs in patients with cGVHD.

**Topical Corticosteroids**

Topical steroids provide high ocular surface drug concentrations and are able to promote lymphocyte apoptosis and suppress cell-mediated inflammation. Topical steroids (prednisolone acetate 4 X per day) have been shown to reduce inflammatory activity in cicatricial conjunctivitis and related symptoms without having an effect on tear production. They are indicated in acute exacerbation of ocular cGVHD and can also be used in other inflammatory cGVHD-related conditions (eg, episcleritis). Treatment with topical corticosteroids must be managed by an ophthalmologist to monitor side effects such as ocular hypertension and glaucoma, cataract formation, corneal thinning, and infectious keratitis. Rimexolone and fluorometholone seem to provide a lower risk of steroid-induced secondary glaucoma compared with prednisolone acetate (and their use may therefore be beneficial in children), but their therapeutic potential has not been evaluated in ocular cGVHD up to now. The use of topical corticosteroids should be restricted to short-term treatment and low frequency if possible; long-term anti-inflammatory treatment should rather be performed with cyclosporine eye drops as described above if tolerated by the patient. In cases of (persistent) epithelial

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**TABLE 7. Quality of Evidence Supporting the Recommendation**

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Definition of Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from ≥1 properly randomized controlled trial(s)</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from ≥1 well-designed clinical trial(s) without randomization, from cohort or case-controlled analytic studies (preferable from &gt;1 center), or from multiple time series or dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees</td>
</tr>
<tr>
<td>III-1</td>
<td>Several reports from retrospective evaluations or small uncontrolled clinical trials</td>
</tr>
<tr>
<td>III-2</td>
<td>Only 1 report from small, uncontrolled, clinical trial or retrospective evaluations</td>
</tr>
<tr>
<td>III-3</td>
<td>Only case reports available</td>
</tr>
</tbody>
</table>

Qualifier for categories I and II: (a) evidence derived directly from study(s) in GVHD and (b) evidence derived indirectly from study(s) in analogous or other pertinent disease.

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**FIGURE 1.** Ocular cGVHD manifestation at the lids: anterior and posterior blepharitis with obstruction of the meibomian glands (arrows) at the lid margin (A), periorcular erythema and irregular pigmentation, pseudoptosis of the upper lid, and telangiectasias of the lid margin (B). Ocular cGVHD manifestation at the conjunctiva: pseudomembranous conjunctivitis in a patient with severe cGVHD with acute onset: the pseudomembrane is visible in the lower fornix (C), inflammation of the bulbar conjunctiva, and the conjunctiva of the fornix with redness (hyperemia) and mucous secretion (D).
defects or ulcers of the cornea, topical steroids should be avoided (or used with extreme caution) because of the increased risk of infections, impairment of epithelial healing capacity, and risk of corneal thinning in patients with ocular cGVHD. In the survey among German, Austrian, and Swiss transplant centers, topical steroids are frequently applied in ocular cGVHD by 12 of 31 responding centers, another 8 use them occasionally, and 3 use them infrequently.

**Systemic Anti-Inflammatory Therapy**

Systemic immunosuppressants such as cyclosporine can be effective for treating ocular cGVHD including lacrimal

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**FIGURE 2.** Ocular cGVHD manifestation at the conjunctiva: conjunctival scarring with sub-tarsal fibrosis of the lower (A, B) and upper tarsus (C) in ocular cGVHD. Cicatricial occlusion of the lacrimal puncta leading to lacrimal outflow obstruction (D).

**FIGURE 3.** Corneal involvement of cGVHD: Corneal sloughing and filamentary keratitis (A, B) are typical signs of cGVHD and the pronounced superficial punctate keratopathy, more clearly visible after application of fluorescein stain (C). Corneal scarring after corneal ulceration in severe ocular cGVHD (D).
Systemic immunosuppression is not generally prescribed for patients whose sole manifestation is ocular cGVHD as it may negate the overall graft-versus-tumor effect and decrease patient survival because of side effects. However, dose reduction or cessation of systemic immunosuppressive therapy in patients with systemic cGVHD can result in acute exacerbation of ocular cGVHD: If the inflammatory activity of ocular cGVHD cannot be controlled by topical treatment alone (see above), systemic immunosuppressive therapy has to be adapted.2

New therapeutic approaches such as extracorporeal photopheresis seem to improve ocular involvement in cGVHD although controlled prospective studies are required.4 Systemic low-dose tetracycline or doxycycline reduces inflammatory activity in blepharitis18 and seems to be beneficial in cGVHD-associated blepharitis. Intake of omega-3 fatty acids (eg, flaxseed oil 2000 mg per day) may be also effective in reducing inflammation in blepharitis, but the effect has not been confirmed in randomized trials yet.39,40

Oral medications, which increase aqueous tear flow, are selective muscarinic agonists such as pilocarpine and cevimeline. They have been shown to improve KCS in patients with Sjögren syndrome43,44 and may be effective in patients with cGVHD,7 but contraindications and side effects have to be considered.2

Autologous Serum Eye Drops

Autologous serum eye drops can be very effective in patients with ocular cGVHD; their therapeutic effect has been shown in case series and case-control studies in ocular cGVHD and in non–GVHD-related severe ocular surface diseases.45–50 A randomized, placebo-controlled, clinical trial of autologous serum eye drops in cGVHD is about to start at the National Eye Institute. Autologous serum eye drops provide several advantages compared with artificial tears because of their components (epitheliotrophic growth factors, cytokines, nerve growth factors, vitamins) and their biomechanical properties (similarity to natural tear film, no preservatives), although theoretically could accelerate disease by untoward antigen–antibody complex formation. They are not only very effective as lubricants but may also affect the disease course through anti-inflammatory and nutritive effects on the ocular surface as they contain interleukin-1 receptor antagonists, tissue inhibitors of matrix metalloproteinases, and immunoglobulin G and complemet factors.51

Treatment with autologous serum eye drops must be performed according to the local legal regulations for drugs and for blood products and transfusions and is therefore limited to specialized centers.52 Contraindications for autologous serum treatment such as systemic bacterial or viral infections, and so on,52 have to be considered and possible interactions of systemic medications that are present in the serum of patients with cGVHD. Umbilical cord serum eye drops and allogeneic serum eye drops may be an alternative treatment option.53,54 Proper mechanisms to prevent infections must be implemented with any use of serum eye drops including appropriate storage.52,55

Control of Evaporation

Meibomian gland dysfunction can be improved by regular application of warm compresses (2–3 × per day for 10 minutes) and lid care with ointment or solution (eg, 2–3 × per day) during the post-acute or chronic phase.56 Topical antibiotic ointment (eg, doxycycline, tetracycline) or eye drops (eg, azithromycin)
Systemic treatment with low-dose oral steroids tends to be lost frequently, especially if the size of the plug is not appropriate for the patient. Permanent punctal occlusion by thermal cautereization or surgical occlusion of the puncta can be performed when punctal plugs are beneficial for the patient but have to be used with care in the acute phase because tear production can recover during the course of disease.

**Scleral Lenses**

Scleral contact lenses can be very successful in ameliorating the symptoms in patients with severe ocular cGVHD and are able to improve the quality of life dramatically in some patients. Up to now, scleral contact lenses have been available only in selected centers.

**Prevention of Infectious Disease**

In cases of epithelial defects, topical antibiotic agents are mandatory; if possible, preservative-free antibiotic eye drops with low epithelial toxicity are preferred (eg, ofloxacin). Some authors recommend anti-herpetic therapy as prophylaxis for herpes simplex–seropositive patients under topical immunosuppressive treatment.

**Management of Complications**

Surgical approaches are necessary in severe cases of ocular cGVHD. In filamentary keratitis, superficial debridement can improve epithelial healing. In cases of pseudomembranous conjunctivitis, excision or removal of pseudomembranes may be beneficial for epithelial recovery. Autologous serum eye drops are often effective for the treatment of corneal epithelial defects because of their epitheliotropic properties (see above). Bandage contact lenses can be helpful as short time therapy (in combination with prophylactic treatment with topical antibiotics). For refractory epithelial defects and corneal ulcers, amniotic membrane transplantation can promote corneal healing and prevent further corneal thinning and perforation.

**CONCLUSIONS**

Ocular involvement in cGVHD is common in the long-term follow-up of patients after HSCT and is frequently related to morbidity and significant reduction in quality of life. Therefore, prevention, diagnosis, treatment, and supportive care of ocular cGVHD are important components of multidisciplinary post-HSCT management.

The Consensus Conference on Clinical Practice in Chronic GVHD tried to summarize the current status in diagnosis and treatment of ocular cGVHD and to provide practical guidance for clinical practice. Ocular cGVHD is typically considered a disease of the conjunctiva and lacrimal glands, whereas the frequent present involvement of the lid and meibomian glands seems to be underestimated up to now. It is important to realize that ocular cGVHD is not only related to dryness of the ocular surface but also related to excessive and ongoing inflammatory activity and scarring in many patients. To date, there have been no specific clinical signs identified for ocular cGVHD, which may be diagnostic for ocular cGVHD. However, the presence of distinctive features of ocular cGVHD including reduced Schirmer scores in combination with (1) manifestation of cGVHD in other organs (especially involving mucosal and glandular tissues) or (2) a positive conjunctival biopsy (showing signs of lymphocytic infiltration, lymphocyte exocytosis, epithelial cell necrosis, saturation, vacuolization of the basal epithelium, reduced goblet cell density, epithelial attenuation, and squamous metaplasia) allows for the diagnosis of ocular GVHD.

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Amniotic membrane covered Illig shells as temporary bio-onlay have been described for treatment of persistent epithelial defects, providing the advantage of sutureless application. Surgical approaches to the ocular surface are often combined with a (permanent) partial tarsorrhaphy (see above) to decrease the exposed corneal area and limbal epithelial transplantation and keratoplasty (corneal transplantation) have been described in patients with ocular cGVHD; however, the prognosis is markedly reduced in cases of ongoing dry eye disease and inflammatory conditions. In cases of membranous conjunctivitis with fornix adhesions, the application of an Illig shell may be necessary. For treatment of cicatricial entropion with trichiasis or exposure keratopathy, lid surgery, eventually combined with amniotic membrane or mucus membrane transplantation, can be performed when inflammatory activity has resolved.

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The consensus conference proposes a screening protocol including a baseline examination before HSCT and further ophthalmological assessments at different time points or in case of ocular symptoms and other cGVHD manifestations, respectively (Table 3), in addition to the ophthalmological workup after HSCT proposed by the NIH consensus.

The consensus conference proposes the evaluation of new grading criteria for ocular cGVHD (Table 4) in clinical use in the future. The participants in the consensus conference agreed in recommending a more detailed documentation of ocular cGVHD.
in the NIH GVHD documentation sheet according to the grading criteria and comparable to the documentation for oral cGVHD.\textsuperscript{1} The severity grading of ocular cGVHD developed for clinical studies from the NIH consensus\textsuperscript{3,21} seems to be useful also for clinical practice.

In general, the evidence levels for ocular cGVHD therapy are low. However, the consensus conference tried to summarize reasonable therapeutic strategies (Table 5). The therapeutic management should be interdisciplinary, multi-modal, and individually adapted to the patient’s conditions and age to be as effective as possible. Topical immunosuppression with cyclosporine eye drops represents up to now the only promising topical disease-modifying and long-term strategy to reduce inflammatory activity and to improve lacrimal gland function and goblet cell density. Presently, a clinical trial is underway to evaluate the prophylactic use of cyclosporine eye drops to prevent ocular cGVHD (NCT00755040).

The consensus conference emphasized the need for further studies to improve diagnostic measures, clinical documentation, and grading; to elucidate risk factors of ocular cGVHD; and to evaluate therapeutic concepts. All proposed recommendations have to undergo further evaluation in clinical practice and in clinical studies in the future.

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