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Research Paper

Corneal fluorescein staining and ocular symptoms but not Schirmer test are useful as indicators of response to treatment in chronic ocular GVHD

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ABSTRACT

Purpose: To evaluate long-term ocular surface clinical signs and symptoms response to therapy in patients with chronic ocular GVHD.

Methods: Retrospective review and data modeling. We reviewed the records of post-bone marrow transplantation patients who were newly diagnosed with ocular GVHD and initiated therapy, and analyzed changes in symptoms (Ocular Surface Disease Index [OSDI]; Symptom Assessment in Dry Eye [SANDE]) and signs (corneal fluorescein staining [CFS]; Schirmer test). We used a LOESS technique to fit a model in function of data variations and obtain a predictive value of the scores progression over time.

Results: The records of 123 patients who were followed-up for over 2 years (up to 62 months) were reviewed. The median baseline scores recorded were: OSDI 52 units, SANDE 62.2 units, CFS 2.0 Oxford units, and Schirmer 4 mm. After six months of follow up, scores improved for OSDI (−18.6 units, $p = 0.007$), SANDE (23.7 units, $p = 0.01$), and CFS (−0.7 Oxford units, $p < 0.001$). Data analysis showed that after a 2-year follow up the three parameters continued to improve: OSDI -13.67 units (27% reduction), SANDE -17.55 units (28%), CFS -1.1 units (54%), but Schirmer test scores progressively worsened −1.2 mm (22%).

Conclusion: In patients with ocular GVHD symptoms and corneal fluorescein staining improved after initiation of treatment, meanwhile Schirmer scores declined progressively. This indicates that appropriate treatment in chronic ocular GVHD can lead to mid- and long-term improvements in symptoms and corneal epitheliopathy; however, sustained reduction in Schirmer test scores suggests chronic tear production impairment.

1. Introduction

Chronic graft-versus-host disease (GVHD) has become a major cause of morbidity in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [1–6]. The eye is the most commonly affected organ in patients with chronic GVHD, with an involvement rate of 65% of cases with moderate to severe disease [7,8]. Dry eye disease (DED) associated with chronic GVHD is a major complication, and in some cases the sole feature of chronic GVHD [2,9–11]. However, establishing a diagnosis and scoring of chronic ocular GVHD is sometimes challenging due to limited understanding of its pathophysiology and due to limited understanding of which DED assessment tools are most useful for monitoring disease activity [1].

Symptoms of chronic ocular GVHD typically resemble those seen in dry eye disease, and include dry, gritty or painful eyes, redness or excessive tearing. The pathophysiology of chronic ocular GVHD is thought to be secondary to donor-derived immune cells attacking host tissues [12,13], which leads to inflammation, fibroblastic proliferation, and consequent fibrosis in the periductal areas of the lacrimal and meibomian glands and their secretory apparatus [12,14,15]. This tissue destruction and fibrosis may result in permanent loss of lacrimal and meibomian function that may not improve with treatment. In ocular GVHD affecting the lids and meibomian glands, aqueous output may not be affected. Hence, symptoms and clinical signs of dry eye in ocular GVHD are diverse and can vary from mild to severe [11].

There are limited studies describing long-term changes of dry eye symptoms and clinical signs used to monitor disease activity and treatment outcomes in ocular GVHD [10,16–20]. Some studies have reported lack of correlation between patient-reported symptoms and clinician-reported clinical signs, emphasizing the limitations and complexities of implementing the Schirmer test routinely [19,20]. The NIH Development Project on Criteria for Clinical Trials in Chronic GVHD reported that Schirmer test may be useful for diagnosis but not for follow-up of ocular GVHD due to poor correlation with symptoms [19]. The International Chronic Ocular GVHD Consensus Group recognizes the criteria recommended by transplant physicians to conduct clinical

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Table 1
Patients' topical and systemic therapies for ocular and systemic GVHD.

Local treatments for ocular GVHD
Topical lubricants
Punctal occlusion
Topical cyclosporine
Topical autologous serum
Antibiotic ointment
Topical corticosteroids
Topical Anakinra
Mucolytic (10% N-acetylcysteine) therapy
Scleral lens
Systemic treatments for ocular and concurrent systemic GVHD
Tacrolimus
Sirolimus
Cyclosporine
Methotrexate
Mycophenolate Mofetil
Bortezomib
Corticosteroids
Doxycycline

Table 2
Patients' characteristics.

Primary Disorders	Percentage of patients
Acute Myeloid Leukemia	39%
Non-Hodgkin Lymphoma	16%
Myelodysplastic syndrome	13%
Chronic Lymphoid Leukemia	12%
Acute Lymphoid Leukemia	7%
Chronic Myeloid Leukemia	6%
Multiple myeloma	4%
Hodgkin Lymphoma	1%
Other	2%
Conditioning Regimen	
Total Body Irradiation	39%
Chemotherapy alone	61%
Chronic GVHD	
Skin	78%
Oral	65%
Liver	44%
Gastrointestinal	22%

trials [19], but states that Schirmer test must be assessed simultaneously with dry eye symptoms and ocular clinical signs by the ophthalmologist, in order to evaluate ocular disease severity [1]. Since the publication of both reports, a growing number of clinical reports continue to include Schirmer test scores as part of chronic ocular GVHD assessment. Herein we present a retrospective analysis of the long-term behavior of dry eye symptoms, corneal fluorescein staining and Schirmer test scores after treatment and clinical follow-up for chronic ocular GVHD (See Tabels 1 and 2).

2. Materials and methods

We conducted a retrospective study of patients diagnosed with ocular GVHD after allo-HSCT, at the Cornea Service, Massachusetts Eye and Ear Infirmary (MEEI), Boston, MA. The study was approved by the MEEI Institutional Review Board and followed the tenets of the Declaration of Helsinki.

We reviewed the records of patients diagnosed with ocular GVHD at our institution and from patients referred to our department for treatment, in whom the diagnosis had been made within the previous 90 days and specialized ophthalmological treatment was initiated by us. We included the records of patients with chronic ocular GVHD following the criteria proposed by the International Chronic Ocular GVHD Consensus Group, the National Institutes of Health Ocular GVHD diagnostic criteria, and in accordance with other retrospective reports [1,21]. We included patients who presented with all of the following: 1) history of allogeneic HSCT; 2) new onset of dry eye symptoms (ocular sicca) post-HSCT such as: conjunctival injection, burning, dryness or foreign body sensation; 3) required frequent topical treatment; and 4) at least two of the following clinical signs of ocular surface disease: Schirmer test of ≤ 5 mm, presence of corneal fluorescein staining, and/or a tear beak-up time (TBUT) of ≤ 10 s.

The variables evaluated in this study included common clinical parameters used to assess dry eye disease: Schirmer test score with anesthesia, corneal fluorescein staining (CFS) using the modified Oxford scheme [22], and patient-reported symptoms using the OSDI and the Symptom Assessment in Dry Eye (SANDE) questionnaires. The OSDI (Allergan Inc., Irvine, CA) is a 12-item questionnaire designed and validated to provide a rapid assessment of symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning [23]. The OSDI is scored on a scale of 0–100, where higher scores represent greater disability. The SANDE questionnaire relies on a visual analog scale consisting of two horizontal lines (100 mm) that assess the frequency and severity of dry eye symptoms experienced by the patient, and its score is calculated by obtaining the square root of the product of the frequency and severity scores [24].

2.1. Statistical analysis

We calculated the median and interquartile range of data for continuous variables and the proportions for categorical variables in order to show a more accurate figure of their distribution. We also calculated the means of the data to assess differences between the variables' mean scores at baseline and follow-up visits with a paired *t*-test. Then we used the locally weighted scatterplot smoothening (LOESS) regression analysis to fit a model in function of the variations of the data from all the different visits, and obtain a value for the scores progression over time. This analysis was used to account for missing cases given its ability to compute the deterministic part of the point-by-point variation in the data. Finally, we evaluated the concordance between questionnaires used to assess dry eye symptoms at baseline and throughout the long-term follow-up using the Spearman coefficient of correlation. In the case of variables measured in both eyes a mixed model regression analysis was used to account for paired-eyes correlated measures. A two-sided P value of 0.05 or less was considered statistically significant for all the statistical tests performed.

3. Results

We included 123 patients (67 males and 56 females) with a median age of 53 years (range 22–71 years), 75 patients were evaluated at 12 ± 1.4 months, 26 patients were evaluated at 24 ± 1.8 months, and 10 patients at 48 ± 3 months. The baseline scores for the dry eye parameters investigated were (median [interquartile range]): Schirmer 4 mm (IQR 2–8 mm), corneal fluorescein staining 2.0 Oxford units (IQR 1.0–3.0 units), OSDI 52 units (IQR 31.5–68.4 units), and SANDE 62.2 (IQR 45–81.6 units). The assessment of symptoms using the OSDI questionnaire showed that 71% of the patients presented with severe DED symptoms (OSDI ≥ 33).

After treatment and during the follow-up period the OSDI score declined to a maximum cumulative reduction of 18.6 units at an average of 6 months (95% confidence interval [CI], 5.67–31.61; $p = 0.007$) compared to baseline. At 6 months 64% of the patients showed a mean decrease of 36.5 units (95% CI 25.9–47; $p < 0.0001$). In cases considered as severe at baseline and which improved, the OSDI at 6 months improved more than 14 units. The mixed-model regression