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ORIGINAL RESEARCH

Chronic Ocular GVHD Treatment at Two Locations of a Tertiary Referral Center

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Purpose: To compare baseline characteristics and treatment of chronic ocular graft-versus-host disease (oGVHD) patients in two treatment locations.

Patients and Methods: Patients diagnosed with definite chronic oGVHD between September 1, 2014 and September 20, 2021 at two locations were identified. IRB-approved retrospective chart review was conducted for the following data: demographic information, ocular surface disease index (OSDI), corneal fluorescein staining (CFS), and treatment(s) used. Differences by site were assessed using Pearson's Chi-Square tests and two-sample t-tests; differences by time were assessed using paired t-tests.

Results: At baseline, Clinic 1 (C1) patients had a worse mean OSDI score (47.8 vs 36.3, $p = 0.011$) and CFS in both OD (1.3 vs 0.8, $p = 0.005$) and OS (1.3 vs 0.6, $p < 0.001$) compared to Clinic 2 (C2). Comparing baseline to endpoint, C1 patients experienced an improvement in OSDI (−17.26, $p < 0.001$), CFS OD (−0.50, $p < 0.001$), and CFS OS (−0.51, $p < 0.001$) at C1. Change in OSDI, CFS OD, or CFS OS was not statistically significant at C2. Despite similar follow-up length, C1 demonstrated more clinic visits (10.4 vs 3.4, $p < 0.001$) and more treatment trials (4.9 vs 2.4, $p < 0.001$) compared to C2. Punctal plugs (85.5% vs 61.2%, $p = 0.002$), punctal cautery (69.7% vs 28.6%, $p < 0.001$), topical steroids (72.4% vs 22.4%, $p < 0.001$), and autologous serum tears (AST) (52.6% vs 8.2%, $p < 0.001$) were used more frequently at C1 than at C2.

Conclusion: oGVHD patients at C1 experienced significant improvement in OSDI and corneal fluorescein staining and compared to patients at C2, had more frequent follow-up and use of punctal plugs, punctal cautery, topical steroids, and AST.

Keywords: graft-versus-host disease, GVHD, chronic GVHD, dry eye disease, ocular GVHD, keratoconjunctivitis sicca, KCS

Introduction

Graft-versus-host disease (GVHD) is an immunological response to transplantation in which donor lymphocytes recognize recipient antigens, primarily recipient minor histocompatibility complexes (miHCC), as foreign and react to recipient tissues. Since miHCCs are not included in routine HLA typing, patients undergoing HLA-matched allogeneic hematopoietic stem cell transplants (HSCT) remain at risk for GVHD.[1] GVHD is the most frequent complication of HSCT, occurring in 30–70% of transplant recipients. While it primarily occurs following allogeneic HSCT, it has also rarely been observed after autologous HSCT, solid organ transplantation, and blood product transfusion.[2,3] GVHD can manifest in many organs including the skin, liver, gut, and eye, and can be categorized as acute or chronic. This categorization was historically based on disease course, with onset within 100 days of transplantation classified as acute and onset or continuation of GVHD manifestations after 100 days classified as chronic. In 2005, acute and chronic GVHD were redefined based on clinical manifestations rather than time or duration of disease alone.[4,5]

Acute GVHD typically involves the skin, GI tract, and liver with ocular involvement being limited to less than 10% of allo-HSCT patients.[6] However, 40–90% of allo-HSCT patients with chronic GVHD (cGVHD) may have ocular involvement.[6] Ocular GVHD (oGVHD) can cause great difficulty in activities of daily living and significantly impact

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patients' quality of life.[7,8] Although oGVHD can involve any part of the eye, the most commonly involved site is the ocular surface.[9]

Keratoconjunctivitis sicca (KCS) is a common manifestation of chronic GVHD and is thought to be primarily driven by donor CD4+ and CD8+ T-cell mediated inflammation, epithelial cell apoptosis, and fibrosis of the lacrimal gland.[10–13] Though the active immune effect has regressed, patients frequently experience significant eye discomfort and pain related to severe aqueous deficiency. Patients with oGVHD commonly have low 5-min Schirmer's testing (without anesthesia) which illustrates this tear deficiency, similar to Sjogren's syndrome and Stevens-Johnson Syndrome. Dry eye disease secondary to oGVHD frequently leads to significant decreases in quality of life, but corneal complications such as ulceration or perforation due to inadequate treatment of tear film deficiency are rare.[10] Environmental factors such as tobacco smoke, wind, and dry or particulate-filled environments may exacerbate dry eye symptoms.[12] The primary goal of treatment of ocular complications of GHVD is to protect and conserve corneal epithelial integrity, maximize tear film quantity and quality, and provide symptomatic relief. These strategies help reduce injury and inflammation from aqueous deficiency caused by lacrimal, conjunctival, and meibomian gland scarring, which could lead to corneal scarring or rarely perforation if left untreated. Unfortunately, regenerative therapies that could permanently restore ocular surface tissue physiology and function in severe ocular surface disease, including not only oGVHD but also Sjogren's syndrome, Stevens-Johnson syndrome, and chemical burns, are not currently available.[9] oGVHD treatment generally follows a "stepped care" approach, beginning with simple treatments such as artificial tears and progressing to more intensive modalities. Specific evidence-based treatment protocols for severe KCS related to oGVHD have yet to be defined; thus, variability in treatment can be observed between different practices.

This study describes treatment modality utilization and subsequent response in patient symptoms and clinical signs at two locations of one multi-center tertiary referral center. One location is in an arid climate while the other is located in a seasonally humid, continental climate.[14] By comparing the clinical management and associated outcomes between the two sites, we aim to contribute valuable insights toward the development of evidence-based protocols for ocular GVHD.

Materials and Methods

This retrospective chart review was approved by the Mayo Clinic Institutional Review Board and conducted in accordance with the tenets of the Declaration of Helsinki. As this study analyzed de-identified data, it was exempt from requiring individual patient consent. An Electronic Medical Record data extraction tool was used to identify patients with chronic GVHD using International Classification of Diseases diagnostic coding that were seen in either Clinic 1 (C1) or Clinic 2 (C2) Mayo Clinic Departments of Ophthalmology between September 1, 2014 and September 20, 2021. Patients were excluded if a manual review of records did not confirm a diagnosis of chronic GVHD. C1 is located in Arizona, USA, and C2 is located in Minnesota, USA. C1 oGVHD clinic is staffed by a cornea fellowship-trained ophthalmologist who performs punctal cautery. C2 oGVHD clinic is staffed by two optometrists specializing in scleral lens care. The recently validated international chronic ocular GVHD consensus group (ICCGVHD) diagnostic criteria were utilized in this study.[5,15] These criteria consider the presence or absence of systemic GVHD along with ocular surface disease index (OSDI), Schirmer's test, corneal fluorescein staining (CFS), and conjunctival injection scores to grade the severity of KCS with chronic oGVHD (none, probable, or definite classifications).[15] Only severely affected patients who met criteria for "definite" chronic oGVHD during the study period were included in this analysis.

Records for initial evaluation and all follow-up visits within the study period were reviewed for patients identified with definite chronic oGVHD. Demographic information collected included patient age, patient sex, and vital status. Clinical variables included OSDI score, CFS score, Schirmer's test score, conjunctival injection score, and treatment modality deployed. OSDI and CFS scores were used to grade severity of symptoms and clinical signs, respectively. The following treatment modalities were considered in this study: artificial tears, hot compresses, moisture chambers, punctal plugs, punctal cautery, autologous serum tears, topical steroids, topical immunosuppressants, and scleral lenses. Practice patterns notably differed in that Clinic 1 used synthetic extended temporary punctal inserts whereas Clinic 2 utilized silicone punctal plugs. Topical steroids used by both sites included dexamethasone-tobramycin, prednisolone acetate,

fluorometholone, and loteprednol. Topical immunosuppressants included cyclosporine, lifitegrast, and tacrolimus ointment.

Results are descriptively summarized as counts and percentages for categorical variables and means, medians, and ranges for continuous variables; medians and interquartile ranges are reported for distance of patient residence to clinic location as this data was not normally distributed. Differences in categorical variables between clinics were tested using Chi-square or Fisher's exact tests, as appropriate; differences in proportions are reported with corresponding 95% confidence intervals (CI), using a normal approximation method or exact binomial CI, as appropriate. Differences in continuous variables between clinics were tested using two-sample t-tests, assuming equal or unequal variance, as appropriate; differences in means are reported with corresponding 95% CIs, calculated using pooled or unpooled variance, as appropriate. The last visit at time of data collection was defined as the endpoint; values from the second to last visit were used as the endpoint value if data from the last visit was not available. When calculating length of follow-up, the most recent visit with measurement of any ICCGVHD score component was considered the last visit. Change in clinical symptoms and signs by clinic was reported among patients with values at both timepoints. Differences by time were tested using paired t-tests. $P < 0.05$ was used as the threshold for statistical significance. Statistical analysis was performed using R version 4.2.2.

Results

Patient Demographics

C1 (N = 76) patients had a mean age of 57 years and comprised 49% females and 51% males (Table 1). C2 (N = 49) patients had a mean age of 57 and comprised 18% females and 82% males. Difference in patient sex between the two sites was statistically significant ($p<0.001$). At time of data collection, 17% of C1 patients were deceased while 22% of C2 patients were deceased. Differences in age and proportion deceased were not statistically significant.

Changes in Patient Symptoms and Clinical Signs Over Follow-Up Period

Clinic 1

At baseline, C1 patients had a mean OSDI of 47.8 and a mean CFS of 1.3 OD and 1.3 OS (Table 2). Conjunctival injection at baseline was 1.0 OD and 1.0 OS. Mean Schirmer's scores at baseline were 6.3 OD and 5.9 OS. Mean calculated ICCGVHD scores at baseline were 7.3 OD and 7.2 OS. By last follow-up, mean OSDI was 29.7 and CFS was

Table 1 Demographics

Demographics	Clinic 1 (N=76)	Clinic 2 (N=49)	Difference in means or proportions (95% CI)	*p*-values	Total (N=125)
Age at diagnosis (years)					
Mean (median, range)	57.2 (60, 29.0–78.0)	57.0 (59.0, 25.0–72.0)	0.27 (−3.79, 4.33)	0.8953	57.1 (59.0, 25.0–78.0)
Sex					
Female	37 (48.7%)	9 (18.4%)	0.303 (0.147, 0.459)	**<0.001**	46 (36.8%)
Male	39 (51.3%)	40 (81.6%)			79 (63.2%)
Vital Status					
Alive	63 (82.9%)	38 (77.6%)	0.053 (−0.091, 0.198)	0.459	101 (80.8%)
Deceased	13 (17.1%)	11 (22.4%)			24 (19.2%)

Notes: Bold values indicate significant *p*-value. Two-sample t-tests assuming equal variance for continuous variables, Chi-Square test for categorical variables.
Abbreviation: N, sample size.

Table 2 Baseline Symptoms and Clinical Signs

Symptoms and Clinical Signs- Baseline	Clinic 1 (N=76) [Mean (median, range)]	Clinic 2 (N=49) [Mean (median, range)]	Difference in means (95% CI)	*p*-values	Total (N=125) [Mean (median, range)]
OSDI	n=74				n=123
Mean (median, range)	47.8 (50.0, 0.0–100.0)	36.3 (38.6, 6.2–87.5)	11.52 (2.72, 20.31)	**0.011**	43.2 (43.2, 0.0–100.0)
CFS	n=74 | n=75				n=123 | n=124
OD	1.3 (1.0, 0.0–3.0)	0.8 (0.0, 0.0–3.0)	0.54 (0.17, 0.92)	**0.005**	1.1 (1.0, 0.0–3.0)
OS	1.3 (1.0, 0.0–3.0)	0.6 (0.0, 0.0–3.0)	0.73 (0.35, 1.11)	**<0.001**	1.0 (1.0, 0.0–3.0)
Conjunctival Injection					
OD	1.0 (1.0, 0.0–2.0)	0.4 (0.0, 0.0–2.0)	0.60 (0.42, 0.79)	**<0.001**	0.8 (1.0, 0.0–2.0)
OS	1.0 (1.0, 0.0–2.0)	0.3 (0.0, 0.0–1.0)	0.65 (0.48, 0.83)	**<0.001**	0.7 (1.0, 0.0–2.0)
Schirmer's Score	n=67	n=42			n=109
OD	6.3 (4.0, 0.0–40.0)	5.0 (4.0, 0.0–34.0)	1.33 (−1.59, 4.24)	0.368	5.8 (4.0, 0.0–40.0)
OS	5.9 (3.0, 0.0–40.0)	5.1 (4.0, 0.0–30.0)	0.87 (−1.96, 3.69)	0.543	5.6 (4.0, 0.0–40.0)
ICCGVHD Scores	n=70 | n=71	n=42			n=112 | n=113
OD	7.3 (8.0, 1.0–10.0)	5.5 (6.0, 0.0–9.0)	1.75 (0.95, 2.56)	**<0.001**	6.6 (7.0, 0.0–10.0)
OS	7.2 (8.0, 1.0–10.0)	5.4 (6.0, 0.0–9.0)	1.79 (1.01, 2.57)	**<0.001**	6.5 (7.0, 0.0–10.0)

Notes: Bold values indicate significant *p*-value. Two-sample t-tests assuming equal variance for continuous variables.
Abbreviations: N, sample size; OSDI, ocular surface disease index; CFS, corneal fluorescein staining; ICCGVHD, international chronic ocular GVHD consensus group diagnostic criteria.

0.8 OD and 0.8 OS (Table 3). Mean change (baseline vs endpoint) in mean OSDI (−17.26, $p<0.001$), CFS OD (−0.5, $p<0.001$), and CFS OS (−0.5, $p<0.001$) were statistically significant (Table S1).

Clinic 2

At baseline, C2 had a mean OSDI of 36.3 and a mean CFS of 0.8 OD and 0.6 OS. Conjunctival injection at baseline was 0.4 OD and 0.3 OS. Mean Schirmer's scores at baselines were 5.0 OD and 5.1 OS. Mean calculated ICCGVHD scores at

Table 3 Endpoint Symptoms and Clinical Signs

Symptoms and Clinical Signs- Endpoint	Clinic 1 (N=76) [Mean (median, range)]	Clinic 2 (N=49) [Mean (median, range)]	Difference in means (95% CI)	*p*-values	Total (N=125) [Mean (median, range)]
OSDI	n=70				n=119
Mean (median, range)	29.7 (25.0, 0.0–77.8)	42.0 (41.7, 4.2–85.4)	−12.28 (−19.55, −5.01)	**0.001**	34.8 (33.3, 0.0–85.4)
CFS	n=75 | n=76				n=124 | n=125
OD	0.8 (0.5, 0.0–3.0)	0.7 (0.0, 0.0–3.0)	0.15 (−0.18, 0.48)	0.362	0.8 (0.5, 0.0–3.0)
OS	0.8 (0.5, 0.0–3.0)	0.9 (0.0, 0.0–3.0)	−0.09 (−0.43, 0.26)	0.623	0.8 (0.5, 0.0–3.0)

Notes: Bold values indicate significant *p*-value. Two-sample t-tests assuming equal variance for continuous variables.
Abbreviations: N, sample size; OSDI, ocular surface disease index; CFS, corneal fluorescein staining.

baseline were 5.5 OD and 5.4 OS. At last follow-up, mean OSDI was 42.0 and CFS was 0.7 OD and 0.9 OS. Mean change (baseline vs endpoint) in mean OSDI, CFS OD, and CFS OS were not statistically significant (p-value= 0.076, 0.461, and 0.057, respectively) (Table S2).

Comparison of Baseline Symptoms and Clinical Signs

As might be expected for an arid climate, C1 patients presented with more severe symptomatology and corneal staining than their C2 counterparts. The differences in baseline OSDI, CFS OD, and CFS OS between the two clinics were all statistically significant (p-value= 0.011, 0.005, and <0.001, respectively). Differences in baseline conjunctival injection OD and OS were also statistically significant (both p-values<0.001). Differences in baseline Schirmer's score OD (p=0.368) and OS (p=0.543) were not statistically significant.

Treatment Frequency and Utilization

The mean duration of follow-up for both groups was similar at 111.2 weeks at C1 and 116.2 weeks at C2 (Table 4). C1 patients had an average of 10.4 visits over their follow-up period while C2 patients had an average of 3.4 visits. Additionally, C1 patients received an average of 4.9 different treatments while C2 patients received an average of 2.4 different treatments. Differences in both number of visits and number of different treatments between the two clinics were statistically significant (both p-values<0.001). Median distance of patient residence from clinic was 24.8 miles (IQR

Table 4 Comparison of Management and Treatment Modalities

Treatment Information	Clinic 1 (N=76) [N (%)]	Clinic 2 (N=49) [N (%)]	Difference in means or proportions (95% CI)	*p*-values	Total (N=125) [N (%)]
Length of follow-up (weeks)	n=75				n=124
Mean (median, range)	111.2 (84.6, 8.0–317.6)	116.2 (85.0, 3.4–328.0)	−4.98 (−37.47, 27.50)	0.762	113.2 (84.6, 3.4–328.0)
Number of visits					
Mean (median, range)	10.4 (8.0, 2.0–78.0)	3.4 (3.0, 2.0–8.0)	6.94 (4.60, 9.28)[a]	**<0.001**[b]	7.6 (5.0, 2.0–78.0)
Number of different treatments					
Mean (median, range)	4.9 (5.0, 0.0–12.0)	2.4 (2.0, 0.0–9.0)	2.51 (1.73, 3.30)	**<0.001**	3.9 (3.0, 0.0–12.0)
Treatment Modalities					
Hot Compress	39 (51.3%)	19 (38.8%)	0.125 (−0.051, 0.302)	0.170	58 (46.4%)
Moisture Chambers	9 (11.8%)	9 (18.4%)	−0.065 (−0.196, 0.065)	0.310	18 (14.4%)
Artificial Tears	71 (93.4%)	49 (100.0%)	−0.066 (−0.149, 0.013)[c]	0.079[d]	120 (96.0%)
Topical Steroids	55 (72.4%)	11 (22.4%)	0.499 (0.345, 0.653)	**<0.001**	66 (52.8%)
Scleral Contact Lenses	13 (17.1%)	9 (18.4%)	−0.013 (−0.150, 0.125)	0.856	22 (17.6%)
Autologous Serum Tears	40 (52.6%)	4 (8.2%)	0.445 (0.309, 0.581)	**<0.001**	44 (35.2%)
Punctal Plugs	65 (85.5%)	30 (61.2%)	0.243 (0.085, 0.401)	**0.002**	95 (76.0%)
Punctal Cautery	53 (69.7%)	14 (28.6%)	0.412 (0.248, 0.575)	**<0.001**	67 (53.6%)
Cyclosporine/Lifitegrast/Tacrolimus	40 (52.6%)	22 (44.9%)	0.077 (−0.102, 0.256)	0.343	62 (49.6%)

Notes: Bold values indicate significant p-value. Two-sample t-tests assuming equal variance for continuous variables (except where indicated), Chi-Square test for categorical variables. [a]Confidence interval calculated using unpooled variance. [b]Two-sample t-test for unequal variances. [c]Exact binomial confidence interval. [d]Fisher's exact test.
Abbreviation: N, sample size.

17.0, 77.5) for C1 and 87.4 (IQR 62.6, 241.6) for C2; the difference in median distances was statistically significant ($p<0.001$). Of the treatment modalities studied, statistically significant differences between the two sites in utilization rate existed for autologous serum tears ($p<0.001$), punctal plugs ($p=0.002$), punctal cautery ($p<0.001$), and steroid eye drops ($p<0.001$); C1 had higher utilization rates for all four of these treatment modalities. Differences in utilization rates of hot compresses, moisture chambers, scleral contact lenses, artificial tears, or ocular immune therapy at the two sites were not found to be statistically significant. Use of systemic medications was not analyzed. Complete information regarding treatment utilization rates is presented in Table 4.

Discussion

The primary cause of cGVHD-related KCS appears to be lacrimal gland dysfunction secondary to T-cell mediated inflammation, epithelial cell apoptosis, and fibrosis. Destruction of these glands leads to aqueous tear deficiency, causing dry eye symptoms in patients. Other contributing factors to dry eyes in cGVHD include chemotherapy, radiation therapy, blepharitis, and meibomian gland dysfunction.[12] KCS can present following HSCT without signs of systemic GVHD and has also been reported as a predecessor of systemic disease.[15] Additionally, due to scarring and fibrosis of the accessory and main lacrimal gland, dry eye disease persists years after remission of systemic GVHD and complete resolution is uncommon.[10]

When treating oGVHD, the goal of treatment is to protect the ocular surface by preserving the tear film, providing symptomatic relief, and decreasing inflammation to reduce the risk of corneal or conjunctival scarring.[12] Amparo et al found OSDI and CFS to improve with treatment of oGVHD and demonstrated a significant correlation between these two parameters.[16] In this report, we found that the clinic that utilized a greater frequency of synthetic extended temporary punctal inserts, punctal cautery, topical steroids, and autologous serum tears had greater improvements in OSDI and CFS. These treatments are more aggressive than initial therapy which consists largely of artificial lubrication and environmental modifications. Additionally, it has been reported that a decrease in OSDI by 7.3 units or more is a clinically significant improvement; therefore the decrease in OSDI by 17.3 units observed at C1 is clinically relevant.[17]

Differences in outcomes observed between C1 and C2 suggest that more frequent evaluation and more aggressive therapy may be indicated for patients with GVHD. Patients receiving care in C1 were seen over 3 times as frequently as those in C2 and received some forms of treatment more frequently than patients in C2. Potential reasons for these differences are myriad. C2 patients resided a median of 87.4 miles from the clinic location compared to a median of 24.8 miles for C1 patients. Challenges associated with travel could have affected both frequency and type of care received at C2. Differences in care processes and general clinical structure could also contribute to variations observed between the two clinics. In C2, clinical capacity designated to care for patients with GVHD was limited to two appointments per week, and most patients were unable to schedule appointments for blood draws necessary for autologous serum tears, placement of punctal plugs, or punctal cautery on the same day as their ocular evaluations. In C1, care was provided by a single ophthalmologist who could provide all necessary care for management during the course of a single day. Lack of ability to monitor for adverse effects of steroid use (either due to geographic challenges or lack of clinical capacity for follow-up) may have limited the utilization of topical steroids in C2. Regardless of the reasons for these differences, however, the data presented here strongly suggests that more frequent and aggressive intervention can lead to improved physiological and patient-reported outcomes.

A secondary finding in this report is that patients at C1, which has an arid climate, presented with worse dry eye symptoms and clinical signs than patients at C2, which has a seasonally humid, continental climate. This observation may in part be explained by climatic differences between the two clinics, as there is evidence suggesting factors like humidity, certain pollutants, and temperature are associated with dry eye disease prevalence and severity.[14,18] A 2020 study of non-GVHD dry eye patients by Berg et al found lower humidity levels to be associated with worse CFS and shorter tear break-up-times. However, they did not find a correlation between OSDI and studied environmental factors.[14] While climatic factors may have driven a statistically significant difference in baseline mean CFS between the two clinics, there was no such difference at endpoint, likely reflecting the efficacy of aggressive treatment at C1. It is possible that greater severity of disease among C1 patients at baseline prompted more aggressive treatment in this subset.

Although there are several treatments available for oGVHD, there is not a consensus on a specific treatment algorithm. The need for such a protocol grows as cGVHD patients survive longer and dry eye disease persists years

beyond the resolution of systemic disease.[19] Herein, we discuss several treatment options for dry eye disease in the setting of oGVHD.

Typically, initial treatment comprises artificial tears during the daytime and an ointment at night. Non-preserved artificial tears are preferred over preserved ones due to reported epithelial toxicity with some preservative agents including benzalkonium chloride.[20] Environmental and lifestyle modifications such as avoiding fans, using humidifiers, and reducing exposure to tobacco smoke can help relieve symptoms. Moisture goggles and sealed glasses can also help by limiting airflow and maintaining a humid periocular environment.[20] In patients with significant meibomian gland involvement, lid hygiene and warm compresses are first-line options that target lipid layer deficiency.[12] Many practitioners also use topical steroids as first-line treatment for patients, which can help reduce cicatricial changes in patients with chronic oGVHD and may provide some symptomatic relief.[6,21] However, topical steroids would not be expected to significantly improve tear production in these patients with conjunctival, accessory lacrimal gland, goblet cell, and lacrimal gland scarring. Furthermore, long-term use of topical steroids can put patients at risk of adverse effects such as corneal thinning, neurotrophic corneal ulcers, cataracts, and steroid-induced glaucoma.[12,20] The role of topical steroids is unclear. Their use can provide some symptom relief, but generally, the bulk of GVHD inflammation has subsided, and a scarred and aqueous deficient surface is the aftermath. Careful consideration should be given to the risks and benefits of chronic topical steroids prior to initiation of this therapy.

Punctal plugs can be considered for patients who require additional relief. These are generally effective and well tolerated with rare side effects, and are also easily reversible if epiphora occurs.[22] There is some concern with the use of punctal plugs in inflammatory conditions due to retention of proinflammatory tear components leading to further ocular surface damage.[23] However, Sabti et al did not find punctal occlusion to increase inflammation in oGVHD patients.[24] Additionally, the flange of punctal plugs can rub on the ocular surface especially if puncta are located in an entropic position. Synthetic temporary extended punctal inserts can be considered in patients experiencing irritation or discomfort with silicone plugs. Lastly, plugs can be spontaneously lost, particularly in patients with KCS secondary to oGVHD.[25] If silicone plugs are repeatedly dislodged, cause irritation due to flange rubbing, or result in long-term biofilm coating formation, punctal cautery offers a more long-term solution.[12] Wang et al found that cauterization significantly improved CFS in patients with dry eye disease and that this improvement persisted for more than 12 months. Recanalization and reopening of puncta may occur requiring repeat cauterization, especially in patients younger than 60 years of age. Studies have found recanalization rates between 21% and 25%, although these are reported to be lower in cicatrizing processes like cGVHD.[25–27] Autologous serum tears can be used as an alternative or adjunctive therapy to punctal occlusion and have been shown to provide both subjective and objective improvements in oGVHD patients.[28] These are produced using autologous serum and contain growth factors, cytokines, fibronectin, and vitamin A which help promote ocular surface healing.[6] In addition to lubrication, serum tears may also affect disease course by reducing inflammation and providing nutrition.[20] However, serum tears are not covered by insurance and are a recurring cost to patients.[29] Topical anti-inflammatory drugs such as cyclosporine, lifitegrast, or tacrolimus ointment may be difficult for patients to tolerate but can be used in conjunction with other treatment options and are useful in oGVHD management due to their immunosuppressive effects.[30]

Scleral lenses are an option for those with moderate to severe disease with symptoms not relieved by more conservative options. These rigid, gas-permeable lenses rest on the scleral surface allowing for greater coverage of the ocular surface than soft contact lenses. These lenses allow for continuous protective hydration of the ocular surface via a fluid layer between the cornea and scleral lens, while also improving visual acuity by correcting refractive error and irregular astigmatism. Difficulty with fit may improve by increasing tear film volume before fitting with scleral lenses. Pairing moisture chambers with scleral lenses may be helpful to reduce evaporative effect and improve wear time for scleral lens patients in dry, windy environments. Surgical interventions such as tarsorrhaphy or corneal transplantation are reserved only for severe cases refractory to all other interventions to avoid corneal complications.[12] A patient presenting with corneal ulceration may benefit from temporary tarsorrhaphy.

The findings of this study add to the conversation of efficacious treatment modalities and can help guide future research on which the development of a standardized treatment protocol can be based. A protocol for addressing chronic oGVHD patients is suggested. First, it is important to evert the eyelids and examine for acute inflammation and conjunctival ulcerations to rule out acute oGVHD. Concerns for acute oGVHD should be addressed with the patient's hematologist to evaluate the need for more immune suppression. If patients are tapering off systemic immune suppression, worsening ocular surface disease may signify that

GVHD may be active again. After assessing for the level of chronic oGVHD and classifying it as "none, probable, or definite oGVHD", implement the following and assess in a step-wise manner over a follow-up interval of weeks to months: 1) plugs, 2) autologous serum tears, 3) moisture chambers, 4) punctal cautery, 5) scleral lenses. This suggested protocol may require alteration based on the ability of the patient to return for follow-up and insurance coverage for various forms of intervention. Plugs and punctal cautery are covered benefits, so these may be deployed earlier. Autologous serum tears and scleral lenses are often not accessible by patients either due to financial constraints or because patients cannot locate a local provider. National compounding services can provide serum tears to help patients who live away from their eye care providers.

Limitations

Retrospective chart reviews can be limited by incomplete data in the patient medical records; this study is subject to that limitation. At C2, two providers performed initial exams and interobserver variability in subsequent grading of CFS and conjunctival injection could also be a confounding factor between the sites and within a site. Furthermore, the retrospective design did not allow for control of all variables that may affect patient outcomes, including, but not limited to, severity of initial disease presentation, severity of systemic disease, limited access to care, and lack of financial resources. Further prospective studies are needed to confirm the validity of this report.

Conclusion

Chronic oGVHD is associated with high morbidity and mortality, and eye complaints must be addressed to return cancer patients to an improved quality of life. Treatment of chronic oGVHD patients showed significantly improved clinical signs and decreased symptoms with more frequent and aggressive approaches for KCS in a multimodality stepped approach. Punctal cautery should be considered for severely affected patients with keratitis and low Schirmer's scores. Eye care providers can provide valuable care for patients with chronic oGVHD and should be included as part of their multidisciplinary care teams.

Abbreviations

Graft-versus-host-disease (GVHD), chronic graft-versus-host-disease (cGVHD), ocular graft-versus-host disease (oGVHD), minor histocompatibility complexes (miHCC), keratoconjunctivitis sicca (KCS), Clinic 1 (C1), Clinic 2 (C2), international chronic ocular GVHD consensus group (ICCGVHD), ocular surface disease index (OSDI), corneal fluorescein staining (CFS), confidence interval (CI), hematopoietic stem cell transplantation (HSCT).

Disclosure

No direct conflicting relationship exists for any author. Dr. Patel is a consultant to Santen Inc., Design Therapeutics Inc., Iris Medicine Inc., Invirsa Inc., and Emmecell, had recent consulting activities with GlaxoSmithKline, and developed V-FUCHS, which Mayo Clinic licenses to Santen Inc., Design Therapeutics Inc, Iris Medicine Inc., and Kowa Research Institute. All relationships are unrelated to the topic of the manuscript.

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