DOI: 10.4274/tjo.galenos.2022.50945
Turk J Ophthalmol 2022;52:366-373

Original Article

Age-Related Differences in the Clinical Patterns of Ocular Graft-Versus-Host Disease

Rana Altan-Yaycıoğlu*, Yonca Aydın Akova**, Oya Dönmez***

*Adana Medline Hospital, Clinic of Ophthalmology, Adana, Turkey
**Bayındır Kavaklıdere Hospital, Clinic of Ophthalmology, Ankara, Turkey
***İzmir Tınaztepe University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

Abstract

Objectives: To evaluate age-related differences in clinical patterns of ocular graft-versus-host disease (GVHD).
Materials and Methods: In this cross-sectional study, patients diagnosed with ocular GVHD were evaluated in two groups: Group I included those aged 18 years or younger and Group II included those over 18 years of age. Demographic and clinical information were recorded and compared between the groups.
Results: Forty eyes of 20 patients were included (11 patients were in Group I and 9 patients were in Group II). Follow-up was at least 6 months. All patients had burning, dryness, and foreign body sensation. Conjunctival hyperemia, cicatricial conjunctivitis, and limbal stem cell disease (LSCD) was observed more frequently in Group II. In addition to non-preserved artificial tears, cyclosporine A 0.05% (65%) and autologous/allogeneic serum eye drops (80%) were given and silicone plugs were inserted (28%). In Group I, an improvement in GVHD scoring and best corrected visual acuity was observed after 6 months of treatment ($p<0.0005$).
Conclusion: In ocular GVHD, conjunctival cicatrization and limbal stem cell deficiency might be observed more often in adults. Topical cyclosporine, autologous/allogenic serum drops, and punctal plugs are helpful in moderate or more severe cases. With early diagnosis and treatment, an improvement in clinical signs and visual acuity might be observed, particularly in younger patients.
Keywords: Conjunctiva, cornea, dry eye, graft-versus-host disease, meibomian gland dysfunction

Address for Correspondence: Yonca Akova, Bayındır Kavaklıdere Hospital, Clinic of Ophthalmology, Ankara, Turkey
E-mail: yoncaakova@yahoo.com **ORCID-ID:** orcid.org/0000-0002-0177-9517
Received: 28.11.2021 **Accepted:** 22.01.2022

Cite this article as: Altan-Yaycıoğlu R, Akova Y, Dönmez O. Age-Related Differences in the Clinical Patterns of Ocular Graft-Versus-Host Disease. Turk J Ophthalmol 2022;52:366-373

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is used for many hematologic malignancies and non-malignant disorders. The expansion of indications as well as the success of the procedure has resulted in a rise in the number of procedures performed. Allo-HSCT is thought to work by inducing an immune response to malignant cells.[1] Graft-versus-host disease (GVHD), which can be acute or chronic, is the leading cause of morbidity and mortality following allo-HSCT. Approximately 30-70% of HLA-matched patients develop chronic GVHD.[2] Chronic GVHD is a pleiotropic multi-organ inflammatory syndrome that has the potential to affect all mucosal surfaces, including the ocular, oral, vaginal, and gastrointestinal mucosa.[3]

Ocular involvement is observed in 60-90% of patients with chronic GVHD.[4] The prevalence of ocular GVHD is increasing with improved survival rates after allo-HSCT. Ocular GVHD primarily affects the ocular surface, cornea, conjunctiva, eyelid, and lacrimal gland. According to the diagnostic criteria, the new onset of dry, gritty, or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; and confluent areas of punctate keratopathy are distinctive manifestations of ocular GVHD.[3] Ocular dry eye disease (DED) in ocular GVHD usually develops within 6 to 9 months after allogeneic GVHD.[5] Symptoms include irritation, burning, pain, redness, photophobia, blurred or decreased vision, excessive tearing, and the sensation of having sand or grit in the eyes.

In our clinical practice, we observed some differences in the clinical features of ocular GVHD in children and adults. A previous study on the oral complications of chronic GVHD reported that adult patients develop more extensive symptoms compared to children.[6] Thus, in the present study, we aimed to evaluate the clinical patterns of patients diagnosed with ocular GVHD and investigate differences in the frequency of these patterns by age.

Materials and Methods

In this cross-sectional observational study, patients with a history of allo-HSCT who were referred to the ophthalmology clinic due to eye-related complaints and received a diagnosis of ocular GVHD were evaluated. The study was conducted according to the criteria of the Declaration of Helsinki. Institutional review board approval was obtained (#BTEDK-12/20). Patients were examined between April 2017 and December 2019 by two doctors (R.A.Y. and Y.A.A.) who agreed on the classification criteria of the diagnostic protocols (Table 1).[3] Follow-up of at least 6 months was mandatory for inclusion in the study.

Patients were divided into two groups: children (Group I) and adults (Group II). In our country, patients under the age of 18 years are considered children according to Ministry of Health regulations. Thus, patients who were 18 years or younger were included in Group I, and patients over the age of 18 years were included in Group II. All patients were evaluated for history, subjective complaints, clinical findings, and treatment modalities. Their age, sex, indication for HSCT, relevant medical and ocular history, use of systemic medications, and previous topical ocular treatments were noted. Best-corrected visual acuity (BCVA), slit-lamp and fundus examination findings, and intraocular pressure were recorded. Data were recorded at baseline (day 0) and 6 months (day 180).

According to our observation, ocular GVHD does not necessarily affect both eyes. In a study on ophthalmic studies, it was stated that if inter-eye correlation is low, data obtained from both eyes should be analyzed.[7] Therefore, we decided to include both eyes of the patients for evaluation.

BCVA was measured using Snellen visual acuity charts in decimal values and converted to LogMAR units for statistical comparison.

Subjective symptoms were assessed by asking specific questions about tearing, dry/gritty feeling, burning, irritation, foreign body sensation, redness, subjective pain, photophobia, and blurred vision. The Ocular Surface Disease Index questionnaire could not be used with children and thus was not included in the evaluation. Instead, we asked the patients to grade their symptoms from 0 to 4 (0, no complaints; 1, mild complaints not affecting daily activities; 2, moderate complaints slightly affecting daily activities; 3, severe complaints affecting daily activities; and 4, unable to open eyes due to photophobia and pain).

The ocular surface was evaluated with slit-lamp before and following unpreserved fluorescein application. A yellow barrier filter and cobalt blue illumination was used to evaluate punctate staining of the cornea and conjunctiva. Corneal staining was scored from 0 to 3 as none, mild, moderate, or diffuse. Tear film break-up time (TBUT) was measured, and a value less than 5 seconds was considered abnormal. Aqueous tear production was assessed by Schirmer test without anesthesia.

The prevalence and severity of clinical symptoms and signs were evaluated. The severity of dry eye was evaluated with corneal fluorescein staining, Schirmer test, TBUT, and subjective symptoms, and scoring was performed according to the proposed grading system.[8]

Table 1. Ocular graft-versus-host disease scoring according to the National Institutes of Health consensus development project[3]

Score	Symptoms
Score 0	No symptoms
Score 1	Mild dry eye symptoms not affecting activities of daily living (requiring eye drops OR asymptomatic signs of keratoconjunctivitis sicca)
Score 2	Moderate dry eye symptoms partially affecting activities of daily living (requiring drops >3 times per day OR punctal plugs), without vision impairment
Score 3	Severe dry eye symptoms significantly affecting activities of daily living or unable to work (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by keratoconjunctivitis sicca

Additionally, topical medications used were noted from the patients' records. Some patients received topical autologous/allogenic serum. For preparation, the blood was obtained either from the patient or a relative and was screened using standard tests to check for blood-borne diseases. Under sterile conditions, 20 mL of whole blood was collected by venipuncture of an antecubital vein. The blood was immediately centrifuged at 1500 rpm for 10 minutes to obtain serum. The serum was then diluted with balanced salt solution for a final concentration of 30% and divided into five vials. Patients were instructed to keep four vials in a deep freezer, and the fifth in a freezer at 4 °C. Each vial was used for one week after thawing.

Statistical Analysis

Prevalence rates of clinical signs and symptoms and treatment modalities were given. The study parameters were also compared between the two groups. Comparison was performed with chi-square test or paired Student's t-test, as applicable. A probability value (p) of 0.05 was accepted as clinically significant.

Results

Forty eyes of 20 patients were included. Eleven patients (4 female, 7 male) with a median age of 12 years (mean 11.45±5.07 years, range 3-17) were included in Group I. Nine patients (4 female, 5 male) with a median age of 45 years (mean 44.44±1.64 years, range 25-61) were included in Group II. The mean follow-up time at the ophthalmology clinic was longer in Group I (mean 15.67±18.88 months) compared to Group II (8.82±5.78 months); however, the difference was statistically insignificant (p=0.13, Student's t-test).

In Group I, the indication for HSCT was thalassemia major in 4 patients, acute lymphoblastic leukemia in 3, acute myeloblastic leukemia in 2, and aplastic anemia in 2 patients. In Group II, the indication for HSCT was acute myeloblastic leukemia in 6 patients, acute lymphoblastic leukemia in 1, and aplastic anemia in 1, and myelofibrosis in 1 patient. Stem cells were obtained from related donors for 14 patients (7 patients in Group I and 7 patients in Group II) and matched unrelated donors for 6 patients (4 patients in Group I and 2 patients in Group II). The interval between HSCT and ophthalmic examination was 15.05±12.79 months (range 4-48) in Group I and 23.89±22.48 months (range 8-84) in Group II. Although the interval was longer in Group II, the difference was statistically insignificant (p=0.06, Student's t-test).

The patients' subjective complaints are listed in Table 2. All patients had burning, dryness, and foreign body sensation, and most had photophobia (95%), redness (95%), blurred vision (85%), and tearing (80%). When we investigated the difference in complaints, tearing was significantly more frequent in Group I compared to Group II (p=0.000). Although statistically insignificant, itching was more prevalent in Group II (p=0.067).

The GVHD scoring distribution according to the National Institutes of Health classification (Table 1) is shown in Figure 1.[3] As all patients presented with ocular symptoms, none of the patients was Score 0. Following 6 months of treatment (day 180), the scores were statistically better in Group I (p<0.0005), as 10 patients moved from score 3 to score 2. In Group II, one patient with Score 3 improved to Score 2, and the difference was insignificant (p=0.331).

The BCVA in Group I was 0.49±0.39 at presentation (day 0), which increased significantly to 0.33±0.29 at 6-month (day 180) follow-up (p=0.004). In Group II, although an improvement was observed from 0.23±0.37 at day 0 to 0.16±0.26 at day 180, the difference was not significant (p=0.087).

The clinical findings at presentation are shown in Table 3. Meibomian gland dysfunction (MGD) was present in all except

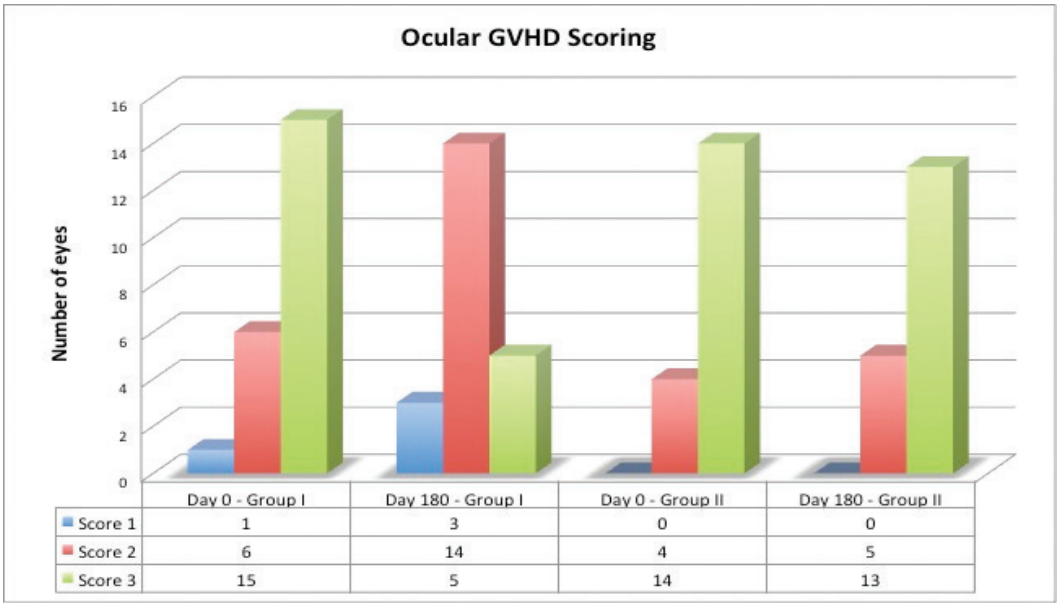

Figure 1. The distribution of cases according to ocular graft-versus-host disease clinical score (number of eyes with each score shown below the graph)

1 patient (95%). Conjunctival hyperemia was observed less often in Group I compared to Group II (p=0.004). Six eyes (15%) had pseudomembrane. Cicatricial conjunctivitis was significantly more frequent in Group II (67% vs. 32%, p=0.028). Limbal stem cell disease was observed only in patients in Group II (44%, p=0.000). Corneal epithelial staining was detected in 36 eyes (90%). The degree of staining was mild in 5 eyes, moderate in 11 eyes, and diffuse in 20 eyes. Five eyes of 5 patients had persistent corneal epithelial defects; 3 of them used bandage contacts for 1 month and the other 2 healed in 2 weeks' time. Five eyes (12.5%) had keratitis. Of these, the etiologic pathogen was bacteria in 3 eyes, herpes virus in 1 eye, and *Candida* in 1 eye.

Table 2. The subjective complains of patients aged 18 years and younger (Group I) and those over 18 years of age (Group II)

	Total (n=40)		Group 1 (n=22)		Group 2 (n=18)		p
	n	%	n	%	n	%	
Photophobia	38	95	22	100	16	89	0.109
Tearing	32	80	22	100	10	56	0.000*
Burning	40	100	22	100	18	100	1.000
Dryness	40	100	22	100	18	100	1.000
Itching	30	75	14	64	16	89	0.067
Foreign body sensation	40	100	22	100	18	100	1.000
Redness	38	95	22	100	16	89	0.109
Pain	10	25	4	18	6	33	0.271
Blurred vision	34	85	20	91	14	78	0.247

n: Number of eyes, *Statistically significant

Table 3. The clinical findings of patients aged 18 years and younger (Group I) and those over 18 years of age (Group II)

	Total (n=40)		Group 1 (n=22)		Group 2 (n=18)		p
	n	%	n	%	n	%	
Periorbital pigmentation	30	75	14	64	16	89	0.067
Trichiasis	1	2.5	1	4,5	0	0	0.360
Ptosis	1	2.5	1	4,5	0	0	0.360
Lagophthalmos	4	10	2	9	2	11	0.832
Conjunctival hyperemia	34	85	14	64	18	100	0.004*
Pseudomembrane	6	15	4	18	2	11	0.533
Cicatricial conjunctivitis	19	48	7	32	12	67	0.028*
Meibomian gland dysfunction	38	95	22	100	16	89	0.109
Filamentary keratitis	16	40	8	36	8	44	0.604
Corneal epithelial staining	36	90	18	82	18	100	0.057
Keratitis	5	12.5	2	9	3	17	0.471
Limbal stem cell disease	8	20	0	0	8	44	0.000

n: Number of eyes, *Statistically significant

During follow-up, cataract developed in 4 eyes of 2 patients in Group II (53 and 61 years of age). In addition, intraocular pressure was elevated in 2 eyes in Group II, one with herpetic and the other with fungal keratitis.

The management strategies are shown in Table 4. All eyes were prescribed frequent non-preserved artificial tears, 18 eyes (45%) received lubricant gels, and 10 (25%) were given eye drops containing coenzyme Q10 (Visudrop®, Visufarma). Short-term loteprednol was used at the start of cyclosporine A therapy to relieve complaints of burning and hyperemia. A total of 26 eyes (65%) received cyclosporine 0.05% (Restasis®, Allergan or Depores®, Deva), 26 eyes (65%) used a dexpanthenol-containing gel (Recugel®, Bausch&Lomb), and 6 eyes (15%) received topical matrix regenerating agent (Cacicol®, Laboratories Thea). Oral doxycycline was given only to Group II in 44% of patients.

Overall, 32 eyes (80%) were given autologous/allogeneic serum eye drops, which resulted in improvement in corneal epithelial problems. In Group II, autologous serum was used in 16 eyes (89%). In Group I, allogeneic serum was preferred because some children were afraid of venipuncture and some were underweight. Therefore, allogeneic serum was used in 16 (73%) of the eyes in Group I.

In Group II, temporary or silicone punctal plugs were inserted in 11 patients, amniotic membrane transplantation was performed in 1 eye with fungal keratitis, and cataract surgery was performed in 4 eyes of 2 patients.

Table 4. The recommended treatment for patients in our study group

	Total (n=40)		Group I (age ≤18) (n=22)		Group II (age >18) (n=18)		p
	n	%	n	%	n	%	
Artificial tears (polyvinyl + povidone, or sodium hyaluronate, or trehalose)	40	100	22	100	18	100	1
Sodium hyaluronate + lipid components	8	20	6	27	2	17	0.203
Carbomer gel	24	45	18	82	6	33	0.002*
Coenzyme Q10	10	25	8	36	2	17	0.067
Dexpanthenol	26	65	12	55	14	78	0.125
Cyclosporine A 0.05%	26	65	10	45	16	89	0.180
Cacicol®	6	15	0	0	6	33	0.003*
Moxifloxacin	22	55	10	45	12	67	0.180
Loteprednol	28	70	10	45	18	100	0.0002*
Tetracycline	8	20	0	0	8	44	0.0005*
Autologous/allogenic serum	32	80	16	73	16	89	0.204
Punctual plugs	11	28	0	0	11	61	0.00002*

n: Number of eyes, *Statistically significant

Discussion

Ocular GVHD can affect the whole lacrimal functional unit, leading to lacrimal gland dysfunction, MGD, and ultimately dry eye syndrome as a result of reduced tear production, excessive tear evaporation, and associated corneal and conjunctival inflammation.[9] In the present study of patients with ocular GVHD, MGD and DED were observed in patients approximately 19 months after allo-HSCT. Although the clinical features were similar at all ages, conjunctival hyperemia, cicatrization, and limbal stem cell disease were more frequent in Group II, which consisted of patients older than 18 years of age. Topical treatment was started immediately with non-preserved artificial tears, and cyclosporine A 0.05% and autologous/allogeneic serum were given when necessary. This treatment approach assisted in the improvement of symptoms, clinical findings, and BCVA, with statistically significant improvements seen in Group I.

The lacrimal gland is one of the organs most susceptible to damage caused by chronic GVHD. In the initial phase, T-cells and other inflammatory cells preferentially target the medium-sized ducts in the lacrimal gland. Immune-mediated fibrosis frequently obstructs the ducts of lacrimal and meibomian glands, as well as the nasolacrimal duct.[9] An increase in stromal fibroblasts, fibrosis of the glandular interstitium, T-cell infiltration of the periductal area, and activation of fibroblasts have been observed.[10] Extensive destruction of the lacrimal gland, including ductal fibrosis, ductular stenosis, and reduced secretory capacity, leads to tissue atrophy.[11] The disease process involving destruction and fibrosis of the conjunctival and lacrimal glands contributes to decreased production of aqueous and mucinous tears, resulting in keratoconjunctivitis sicca.[12]

The most reported symptom of ocular GVHD is dry eye, which typically develops 6 to 9 months after allogeneic HSCT.[5] The interval between HSCT and ophthalmic examination ranged between 4 and 84 months in our study group (mean 19.03±18.12 months). The timing of the development of chronic GVHD was proposed to correspond to the tapering or discontinuation of immunosuppressive treatment.[13] Signs and symptoms include fluctuating vision, burning, foreign body sensation, pain, red irritated eyes, photophobia, and excessive tearing.[11] Similarly, all patients in our study had burning, dryness, and foreign body sensation, and most had photophobia, redness, blurred vision, and tearing. Interestingly, tearing was significantly more prevalent in younger patients, which is probably related to their reserve tear capacity.

Dry eye in ocular GVHD commonly presents with blepharitis and MGD.[14] The prevalence of meibomian gland involvement, with inflammatory cell infiltration, fibrotic changes, and ductal obstruction, was reported as 47.8%.[9] In the present study, MGD was observed in 95% of our patients. Our numbers are probably higher because we included only patients who were already diagnosed with ocular GVHD. Chronic ocular GVHD is an immunological process that may affect the meibomian gland structure more severely than other types of dry eye.[15] Ductal epithelial destruction due to lymphocyte aggregation, epithelial cell sloughing with lymphocyte infiltration, or pseudomembrane formation, and eventual extensive fibrosis around the meibomian gland orifices, ductules, ducts, and acini are observed.[16] On meibography, Hwang et al.[17] showed that aggressive destruction of the meibomian glands leads to meibomian gland loss in more than 80% of eyes.

Conjunctival involvement occurs in 9-41% of cases and is considered a sign of severe systemic impairment of chronic GVHD.[18] Conjunctival hyperemia, chemosis, and pseudomembrane formation are frequent in ocular GVHD.[19] Pseudomembranous conjunctivitis (grade 3) has been reported in 12-17% of patients. We encountered conjunctival hyperemia in 85% and pseudomembrane formation in 15% of our patients with ocular GVHD. Hyperemia was observed in all patients in Group II (>18 years of age) and was significantly more frequent than in the younger patients (Group I). Decreased goblet cell density, increased squamous metaplasia, severe goblet cell loss, and inflammatory cells were observed in the conjunctival biopsy of these patients.[20] We also observed cicatricial conjunctivitis in 48% of all eyes and more frequently in Group II (67%). Cicatrization of the conjunctiva may be palpebral, tarsal, or forniceal, leading to obliteration of the fornices, symblepharon formation, lid scarring, and extensive altered lid anatomy, including trichiasis, entropion, or ectropion development, lagophthalmos, eyelash loss, and lacrimal punctal stenosis.[21]

MGD aggravates ocular surface dryness by increasing tear film evaporation.[22] Therefore, DED with MGD leads to secondary conjunctival subepithelial changes, corneal epithelial changes as punctate keratopathy, filamentary keratitis, painful erosions, and secondary corneal infections. Less frequently, sterile corneal stromal necrosis and perforations have been reported.[2] Corneal fluorescein staining is recommended to diagnose and grade ocular GVHD.[8] Superficial punctate keratopathy is the most common corneal manifestation, as observed in 90% of our patients. Corneal neovascularization, persistent epithelial defects, corneal ulceration, and even perforation are reported.[19] *In vivo* confocal microscopy studies of ocular GVHD demonstrated higher density of dendritic cells and globular immune cells, a hyperreflective activated keratocyte network, and a lower density and higher tortuosity of sub-basal corneal nerves.[23] We observed keratitis in 12.5% of our patients, which was related to secondary infection and epithelial sloughing. Interestingly, limbal stem cell disease was observed only in Group II, accounting for 44% of the patients.

Treatment of ocular GVHD aims to reduce symptom severity, sustain disease activity control, and prevent tissue damage and disability.[24] Stepwise treatment is recommended, beginning with the simplest treatment and transitioning to increasingly aggressive interventions as needed. This approach can be listed as lubrication, tear preservation, prevention of tear evaporation, inflammation reduction, epithelial support, supportive care, and surgical intervention.[11]

Intense lubrication with non-preserved artificial tears and viscous ointment at bedtime is important to preserve the integrity of the ocular surface and dilute the inflammatory

mediators in the tear film.[11] Accordingly, every patient in our study was prescribed frequent artificial tear application.

Tear film evaporation can be reduced by improving meibomian gland expressibility with eyelid hygiene, warm compresses, moderate to firm massage, and lid margin cleansing. Topical antibiotic ointments and systemic tetracycline derivatives may provide additional benefits.[25] We used oral doxycycline in 8 eyes. Also, lipid-containing artificial tears could be added to the treatment, as in some of our patients.

Therapeutic options for ocular GVHD include anti-inflammatory agents such as topical corticosteroids and cyclosporine A, autologous/allogeneic serum eye drops, tacrolimus, tranilast, therapeutic contact lenses, and punctal occlusion.[14,26]

Reversible or permanent punctal occlusion may be provided for patients with severe dry eyes. Despite concerns that increased retention time of tears containing inflammatory cytokines may aggravate ocular surface inflammation, it has been shown to be a safe and effective treatment in ocular GVHD patients.[27] Because they are hard to insert and monitor, we did not prefer the use of punctual plugs in younger patients (Group I). However, 61% of adult patients (Group II) did receive punctal plugs.

Topical steroids promote lymphocyte apoptosis and suppress cell-mediated inflammation. They have been shown to be effective in reducing conjunctival inflammation with cicatricial changes in ocular GVHD.[20] However, considering the possible side effects of corticosteroids, they should only be used short term and with low frequency. We only used short-term loteprednol, usually in the commencement period of cyclosporine A.

Cyclosporine A acts via inhibition of T-cell activation and downregulation of inflammatory cytokines in the conjunctiva and lacrimal gland.[28] The reduction of anterior segment inflammation is thought to allow enhanced tear production. Cyclosporine also increases goblet cell density and decreases epithelial cell apoptosis. It was reported to bring about improvement in Schirmer scores, TBUT, and subjective complaints.[29] In a study of 16 patients (32 eyes) with GVHD, dry eye symptoms improved in 62.5% of patients, and corneal fluorescein staining improved in all eyes after 90 days.[30] Malta et al.[31] recommended initiating cyclosporine A prior to allogeneic stem cell transplantation to decrease lacrimal gland inflammation and thereby reduce post-transplant dry eye. Although a logical approach, we believe that further research is needed before integrating preoperative cyclosporine use into the routine treatment regimen. We started topical cyclosporine in mild to moderate cases (65%) and believe that some of the improvement in clinical signs and symptoms was related to its use.

Recently, topical tacrolimus has been shown to reduce local inflammation.[32] Unfortunately, tacrolimus and tranilast are not available for ophthalmic use in our country, so we were unable to use and observe their effects.

Blood-derived eye drops including autologous or allogeneic serum eye drops contain various factors such as epidermal growth factor, vitamin A, transforming growth factor-beta, and fibronectin.[33] Autologous serum eye drops showed marked suppression of apoptosis in the conjunctival and corneal epithelium. Albumin, the major protein in serum, improved ocular surface damage *in vivo,* and prevented apoptosis after serum deprivation in vitro.[34] Successful outcomes of autologous serum eye drops in patients with severe dry eye related to ocular GVHD have been reported. Rocha et al.[35] observed a beneficial effect of autologous serum eye drops in 2 cases with ocular GVHD. In a study of 14 patients with ocular GVHD and severe dry eye, significant improvement in symptom score, corneal staining score, and tear dynamics was observed following treatment with autologous serum eye drops.[36] In our study, 32 eyes (80%) were given autologous/allogeneic serum eye drops. Autologous serum was used in 89% of the eyes in Group II. In cases where autologous serum is not an option because the patient is young, is afraid of venipuncture, or has active systemic inflammation, allogeneic serum eye drops from healthy members are recommended.[37] We also used allogeneic serum in 73% of the eyes of pediatric patients (aged <18 years) in our study (Group I). We observed significant improvement in subjective complaints as well as clinical signs in both groups. A prospective study of allogeneic serum application for 4 weeks demonstrated marked improvement in symptoms and signs of patients with dry eyes related to ocular GVHD.[38] The authors argued that the amount of aqueous tears was not improved because of fibrosis in the lacrimal gland. However, even in moderate to severe cases, increased numbers of goblet cells probably result in improvement of ocular surface condition and dry eye symptoms. We believe that autologous/allogeneic serum could also be used in mild to moderate cases before the disease progresses.

Contact lens use is an option for ocular surface protection. Soft silicone hydrogels have high oxygen permeability, are suitable for extended wear, and can be used as bandage contact lenses. Besides providing symptomatic relief, they also help protect the cornea from frictional forces of the eyelids, the external environment, and tear film evaporation.[2] We used bandage silicone contact lenses in 2 patients for 2 weeks and for a 1-month period for the treatment of corneal epithelial defect. Although we do not have experience with scleral lenses such as the PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) and other commercially available designs, they have been shown to relieve the symptoms of ocular GVHD. These large-diameter rigid gas-permeable lenses cover most of the exposed surface, and the post-lens fluid reservoir provides continuous hydration of the ocular surface.[39]

Surgical interventions such as epithelial debridement, lateral tarsorrhaphy, amniotic membrane transplantation, forniceal reconstruction, limbal stem cell transplantation, and tectonic keratoplasty have been reported in some cases.[11,19] We needed to perform amniotic membrane transplantation in 1 eye and cataract surgery in 4 eyes in Group II.

After 6 months of treatment, clinical scoring and BCVA improved significantly in Group I. While Group II values were also better following treatment, the comparisons did not reach statistical significance. We believe these different results were related to the nature of histopathologic differences between

children and adults. In adults, the disease has a more severe course leading to cicatricial changes of the lacrimal glands, meibomian glands, and goblet cells. In children, these cells likely still have the potential to partially recover if treatment starts early. However, studies on histopathologic evaluation according to age are necessary to support this hypothesis.

The main limitation of our study is the small sample size, as ocular GVHD is a rare and overlooked condition. Further studies with larger sample sizes may help shed more light on the age-related clinical characteristics of this disease.

Conclusion

In conclusion, ocular GVHD is a disabling condition affecting both children and adult patients. It has a wide clinical spectrum from DED to sight-threatening surface inflammation. Patients' responses to topical treatment options are also variable. Non-preserved artificial tears are satisfactory only in mild cases. Topical cyclosporine is helpful in mild to moderate cases. Autologous/allogeneic serum drops should be the treatment of choice in mild to moderate cases. Allogeneic serum drops are also a good alternative in cases where autologous serum is not available. In adults, cicatricial changes such as conjunctival cicatrization and limbal stem cell disease were more common. After 6 months of treatment, pediatric patients showed significant improvement in clinical scoring as well as BCVA. Early diagnosis and intervention are imperative for optimal outcomes.

Ethics

Ethics Committee Approval: Institutional review board approval was obtained (#BTEDK-12/20).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A.Y., Y.A.A., O.D., Concept: R.A.Y., Y.A.A., O.D., Design: R.A.Y., Y.A.A., O.D., Data Collection or Processing: R.A.Y., Y.A.A., O.D., Analysis or Interpretation: R.A.Y., Y.A.A., O.D., Literature Search: R.A.Y., Y.A.A., O.D., Writing: R.A.Y., Y.A.A., O.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Copelan EA. Hematopoietic stem cell transplantation. N Engl J Med. 2006;354:1813-1826.
2. Hessen M, Akpek EK. Ocular graft-versus-host disease. Curr Opin Allergy Clin Immunol. 2012;12:540-547.
3. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D, Cowen EW, Dinndorf P, Farrell A, Hartzman R, Henslee-Downey J, Jacobsohn D, McDonald G, Mittleman B, Rizzo JD, Robinson M, Schubert M, Schultz K, Shulman H, Turner M, Vogelsang G, Flowers ME. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11:945-956.
4. Kim SK. Update on ocular graft versus host disease. Curr Opin Ophthalmol. 2006; 17:344-348.
5. Shikari H, Amparo F, Saboo U, Dana R. Onset of ocular graft-versus-host disease symptoms after allogeneic hematopoietic stem cell transplantation. Cornea. 2015;34:243-247.
6. Fall-Dickson JM, Pavletic SZ, Mays JW, Schubert MM. Oral complications of chronic graft-versus-host disease. J Natl Cancer Inst Monogr. 2019;2019:lgz007.
7. Zhang HG, Ying GS. Statistical approaches in published ophthalmic clinical science papers: a comparison to statistical practice two decades ago. Br J Ophthalmol. 2018;102:1188-1191.
8. Ogawa Y, Kim SK, Dana R, Clayton J, Jain S, Rosenblatt MI, Perez VL, Shikari H, Riemens A, Tsubota K. International chronic ocular graft-versus-host disease (GVHD) consensus group: proposed diagnostic criteria for chronic GVHD (part I). Sci Rep. 2013;3:3419.
9. Ogawa Y, Okamoto S, Wakui M, Watanabe R, Yamada M, Yoshino M, Ono M, Yang HY, Mashima Y, Oguchi Y, Ikeda Y, Tsubota K. Dry eye after haematopoietic stem cell transplantation. Br J Ophthalmol. 1999;83:1125-1130.
10. Ogawa Y, Kuwana M, Yamazaki K, Mashima Y, Yamada M, Mori T, Okamoto S, Oguchi Y, Kawakami Y. Periductal area as the primary site for T-cell activation in lacrimal gland chronic graft-versus-host disease. Invest Ophthalmol Vis Sci. 2003;44:1888-1896.
11. Munir SZ, Aylward J. A review of ocular graft-versus-host disease. Optom Vis Sci. 2017;94:545-555.
12. Hassan AS, Clouthier SG, Ferrera JL, Stepan A, Mian SI, Ahmad AZ, Elner VM. Lacrimal gland involvement in graft-versus-host disease: a murine model. Invest Ophthalmol Vis Sci. 2005;46:2692-2597.
13. Vigorito AC, Campregher PV, Storer BE, Carpenter PA, Moravec CK, Kiem HP, Fero ML, Warren EH, Lee SJ, Appelbaum FR, Martin PJ, Flowers ME; National Institutes of Health. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. Blood. 2009;114:702-708.
14. Riemens A, te Boome L, Imhof S, Kuball J, Rothova A. Current insights into ocular graft-versus-host disease. Curr Opin Ophthalmol. 2010;21:485-494.
15. Choi W, Ha JY, Li Y, Choi JH, Ji YS, Yoon KC. Comparison of the meibomian gland dysfunction in patients with chronic ocular graft-versus-host disease and Sjögren's syndrome. Int J Ophthalmol. 2019;12:393-400.
16. Ban Y, Ogawa Y, Ibrahim OM, Tatematsu Y, Kamoi M, Uchino M, Yaguchi S, Dogru M, Tsubota K. Morphologic evaluation of meibomian glands in chronic graft-versus-host disease using in vivo laser confocal microscopy. Mol Vis. 2011;17:2533-2543.
17. Hwang HS, Ha M, Kim HS, Na KS. Longitudinal analysis of meibomian gland dropout in patients with ocular graft-versus-host disease. Ocul Surf. 2019;17:464-469.
18. Jabs DA, Wingard J, Green WR, Farmer ER, Vogelsang G, Saral R. The eye in bone marrow transplantation. III. Conjunctival graft-vs-host disease. Arch Ophthalmol. 1989;107:1343-1348.
19. Giannaccare G, Pellegrini M, Bernabei F, Scorcia V, Campos E. Ocular surface system alterations in ocular graft-versus-host disease: all the pieces of the complex puzzle. Graefes Arch Clin Exp Ophthalmol. 2019;257:1341-1351.
20. Townley JR, Dana R, Jacobs DS. Keratoconjunctivitis sicca manifestations in ocular graft-versus-host disease: pathogenesis, presentation, prevention, and treatment. Semin Ophthalmol. 2011;26:251-260.
21. Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. Surv Ophthalmol. 2013;58:233-251.
22. Balasubramaniam SC, Raja H, Nau CB, Shen JF, Schornack MM. Ocular graft-versus-host disease: a review. Eye Contact Lens. 2015;41:256-261.
23. Kheirkah A, Qazi Y, Arnoldner MA, Suri K, Dana R. In vivo confocal microscopy in dry eye disease associated with chronic graft-versus-host disease. Invest Ophthalmol Vis Sci. 2016;57:4686-4691.
24. Inamoto Y, Valdés-Sanz N, Ogawa Y, Alves M, Berchicci L, Galvin J, Greinix H, Hale GA, Horn B, Kelly D, Liu H, Rowley S, Schoemans H, Shah A, Lupo Stanghellini MT, Agrawal V, Ahmed I, Ali A, Bhatt N, Byrne M, Chhabra S, DeFilipp Z, Fahnehjelm K, Farhadfar N, Horn E, Lee C, Nathan S, Penack O, Prasad P, Rotz S, Rovó A, Yared J, Pavletic S, Basak GW, Battiwalla M,

Duarte R, Savani BN, Flowers MED, Shaw BE, Petriček I. Ocular graft-versus-host disease after hematopoietic cell transplantation: Expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. Bone Marrow Transplant. 2019;54:662-673.

25. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, Rolando M, Tsubota K, Nichols KK. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011;52:2050-2064.
26. Ogawa Y, Kuwana M. Dry eye as a major complication associated with chronic graft-versus-host disease after hematopoietic stem cell transplantation. Cornea. 2003;22:S19-S27.
27. Sabti S, Halter JP, Braun Fränkl BC, Goldblum D. Punctal occlusion is safe and efficient fort he treatment of keratoconjunctivitis sicca in patients with ocular GvHD. Bone Marrow Transplant. 2012;47:981-984.
28. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five-year review. Cornea. 2000;19:644-649.
29. Rao SN, Rao RD. Efficacy of topical cyclosporine 0.05% in the treatment of dry eye associated with graft versus host disease. Cornea. 2006;25:674-678.
30. Lelli GJ Jr, Musch DC, Gupta A, Farjo QA, Nairus TM, Mian SI. Ophthalmic cyclosporine use in ocular GVHD. Cornea. 2006;25:635-638.
31. Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A, Mian SI. Treatment of ocular graft-versus-host disease with topical cyclosporine 0.05%. Cornea. 2010;29:1392-1396.
32. Abud TB, Amparo F, Saboo US, Di Zazzo A, Dohlman TH, Ciolino JB, Hamrah P, Dana R. A Clinical Trial Comparing the Safety and Efficacy of Topical Tacrolimus versus Methylprednisolone in Ocular Graft-versus-Host Disease. Ophthalmology. 2016;123:1449-1457.
33. Geerling G, Maclennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. Br J Ophthalmol. 2004;88:1467-1474.
34. Kojima T, Higuchi A, Goto E, Matsumoto Y, Dogru M, Tsubota K. Autologous serum eye drops for the treatment of dry eye diseases. Cornea. 2008;27 Suppl 1:S25-S30.
35. Rocha EM, Pelegrino FS, de Paiva CS, Vigorito AC, de Souza CA. GVHD dry eyes treated with autologous serum tears. Bone Marrow Transplant. 2000;25:1101-1103.
36. Ogawa Y, Okamoto S, Mori T, Yamada M, Mashima Y, Watanabe R, Kuwana M, Tsubota K, Ikeda Y, Oguchi Y. Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. Bone Marrow Transplant. 2003;31:579-583.
37. Chiang CC, Lin JM, Chen WL, Tsai YY. Allogeneic serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. Cornea. 2007;26:861-863.
38. Na KS, Kim MS. Allogeneic serum eye drops for the treatment of dry eye patients with chronic graft-versus-host disease. J Ocul Parmacol Ther. 2012;28:479-483.
39. Jacobs DS, Rosenthal P. Boston scleral lens prosthetic device for treatment of severe dry eye in chronic graft versus host disease. Cornea. 2007;26:1195-1199.