ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Research Article

The Use of 0.005 mg/mL Spironolactone Ophthalmic Solution in Ocular Graft-Versus-Host Disease

Calvin Wayne Wong[1] , Yinuo Liu[2] and Richard Willington Yee[3]*

[1]*Department of Biological Sciences, Rice University, Houston, TX, United States*

[2]*Department of Zoology, St. Anne's College, University of Oxford, Oxford, United Kingdom*

[3]*Department of Ophthalmology, M.D. Anderson Cancer Center, Houston, TX, United States*

***Corresponding Author:** Richard Willington Yee, Department of Ophthalmology, M.D. Anderson Cancer Center, Houston, TX, United States.

Received: May 04, 2021; **Published:** June 28, 2022

Abstract

Ocular involvement in GVHD may include keratoconjunctivitis sicca, sterile conjunctivitis, corneal epithelial lesions, ulcers, and melting. Conventional therapies like lubrication and warm compresses are aimed at treating impaired lacrimal and meibomian gland function and ocular surface defects. The purpose of this study was to show the possible benefit of 0.005 mg/mL spironolactone ophthalmic solution as an adjunct in controlling ocular surface defects in cases of ocular GVHD (oGVHD) resistant to conventional therapy. This retrospective chart review of three chronic GVHD patients with limited response to conventional therapy documents the role of spironolactone in managing oGVHD-related dry eye. Patient presentation commonly included mild to moderate epithelial erosion and reflex tearing. Systemic therapy for GVHD consisting of systemic immunosuppressants (i.e. corticosteroids and tacrolimus) was found to be inadequate to control symptoms and signs of oGVHD. Spironolactone ophthalmic solution was added to conventional treatments and signs and symptoms of oGVHD were recorded. The addition of 0.005 mg/mL spironolactone ophthalmic solution helped in managing the corneal defects, inflammation and dry eye symptoms. Further randomized, masked, controlled prospective study is needed to evaluate efficacy of spironolactone ophthalmic solution in managing oGVHD.

Keywords: *Ocular; Graft-Versus-Host-Disease (GVHD); Spironolactone Ophthalmic Solution; Hematopoetic Stem Cell Transplant (HSCT)*

Background/Aims

Graft-versus-Host Disease (GVHD) is a common complication arising from hematopoetic stem cell transplant (HSCT). While advances in prophylactic treatment and transplant technology have significantly improved patient outcomes, GVHD remains a leading cause of morbidity and mortality following HSCT [1-3]. The acute form of GVHD (aGVHD) is classically characterized by skin involvement including erythema and macropapular rash, hepatic involvement (i.e. cholestatic liver dysfunction), and/or gastrointestinal involvement, including severe diarrhea, nausea, vomiting, and anorexia [1,2,4,5]. Acute GVHD usually develops 3 - 4 weeks post allogenic HSCT, while incidence varies with age and ranges from 25% to 80% [6]. In contrast, chronic GVHD (cGVHD) typically develops 3 - 6 months post allogenic HSCT, has an incidence between 30% to 50% [6-8] and may be characterized by manifestations in the skin, mouth, eyes, and esophagus [2].

Although relatively poorly understood, the pathophysiology of cGVHD is distinct from that of aGVHD: while the acute form can generally be described as a cytokine storm arising from interactions between donor T-cells and host antigen-presenting cells, the chronic form

involves thymic dysfunction and consequent presence of autoreactive T-cells [1,2,9]. The chronic form therefore resembles autoimmune disorders and can be described as a Sjögren-like syndrome [10,11].

Ocular manifestations of GVHD occur in 40% to 60% of patients, and incidence ranges from 50% to 90% in patients who already show systemic signs of GVHD [1,3]. Scleroderma-like changes may manifest in the eyelid, and vitiligo, entropion, and lagophthalmos may develop [4,10]. Corneal changes may include filamentary keratitis, punctate keratitis, ulceration, peripheral melting and perforation [4,12]. Other ocular manifestations include retinal microangiopathy, hemorrhage, lipid deposits, and optic disc edema [10,13,14]. Ocular involvement in aGVHD is rare relative to cGVHD [15], but correlates with poorer survival [2]. More severe ocular manifestations of GVHD, such as pseudomembranous conjunctivitis and corneal melting, correlate with severe systemic cGVHD and poorer prognosis [16].

Keratoconjunctivitis sicca is the most common ocular manifestation of GVHD2, with an incidence of 76% in aGVHD cases and 69% to 77% of cGVHD cases [2,17,18]. In the case of aqueous-deficient dry eye, lymphocytic infiltration of the lacrimal glands results in fibrosis of lacrimal ductules and acini [4,19]. T-cell mediated cytotoxicity may damage periductal cells, further impairing lacrimal gland function [19]. Immunosuppressive therapy, total body irradiation, post-HSCT immune processes, and meibomian gland disease may also contribute to the sicca syndrome, although both the pathophysiologies of these aspects and their interactions remain poorly elucidated. Development of lacrimal dysfunction in GVHD is often irreversible, with limited to no response to treatment of underlying acute or chronic GVHD [13,20].

Severity and extent of ocular involvement in GVHD is generally determined from clinical findings of lacrimal function, bulbar conjunctival injection, fluorescein staining of the cornea, and patient symptoms [21]. In addition, evaluation of hyperemia of the palpebral conjunctiva, lid margin, and of meibomian gland dysfunction may help to develop a better understanding of which tissues are more severely affected.

Effective clinical treatment of ocular surface manifestations of GVHD is often multifactorial. Integrity of the aqueous tear film may be preserved by artificial tears and punctal occlusion, while topical cyclosporine, steroids, and autologous or allogeneic serum control inflammation and surface apoptosis with mixed success [12,22-25]. Treatments for maximizing meibomian gland function have helped to stabilize the tear film and minimize evaporative loss [26]. More aggressive treatments include eye patching, conjunctival flap, and tarsorrhaphy [14,27]. Should these procedures prove ineffective, abnormalities may develop into severe defects such as corneal perforation and/or symblepharon.

Methods

Based on quality of documentation and extent of confounding treatments and conditions, we selected and followed three patients with mild to moderate ocular GVHD with little ocular response to conventional systemic immunosuppressive treatment. These patients were referred from the MD Anderson Cancer Center to the ophthalmology department for evaluation once they had been diagnosed with systemic GVHD based on skin biopsy or elevated liver enzymes. In general, patients usually were treated with conventional topical agents such as artificial tears, Xiidra®, Restasis®, steroids, and/or autologous serum. If patients were not responsive to conventional treatment, patients were started with topical spironolactone, 0.005 mg/mL. spironolactone ophthalmic solution was added in a dose of one drop four times per day. The ocular symptoms and signs of oGVHD, including symptoms of reflex tearing and discomfort, corneal abnormalities and conjunctival inflammation were recorded. Posterior blepharitis as measured by central lid margin vascularity (V), obstruction of meibomian gland orifices (O) and turbidity of meibum (T) were graded from 0 to 4 [28].

Results

Case 1

A patient in their 50s with a history of diabetes, hyperlipidemia, hypertension, and AML underwent HSCT in June 2018. Prior to the operation, the patient was examined and had mild dry eyes, with an unanesthetized Schirmer score of 10 mm OU, tear breakup time of 7 seconds OU, and no complaints of dryness or discomfort. The patient began use of artificial tears as needed. Uncorrected visual acuity was 20/20 OU, with no significant changes immediately after transplant.

Five months post HSCT and subsequent immunosuppressive therapy with tacrolimus, the patient complained of irritation, persistent watering, and blurred vision in both eyes. Uncorrected visual acuity was slightly worsened as measured at 20/20 -2 OD and 20/30 OS. Lissamine staining was present bilaterally across both the bulbar, upper, and lower palpebral conjunctivae, and fluorescein revealed diffuse fine punctate staining, with tear breakup time reduced to 4 and 5 seconds. Tear production was measured at 8 mm OD and 6mm OS. The patient started use of artificial tears and nighttime ointments.

At 9 months post-transplantation, the patient developed more extensive erosion of the cornea, with confluent fluorescein staining OS. Complaints of watering and blurred vision persisted, with tear production increased to 20 mm OD and 15 mm OS. Tear breakup time was 4 seconds bilaterally. Visual acuity was worsened to 20/25 OD and remained at 20/30 OS.

Fourteen months post HSCT, reflex tearing was increased as measured at 30 mm OD and 25 mm OS. V/O/T score was recorded at 1/2/2 OU, suggesting obstructive meibomian gland disease, a diagnosis of non-aqueous dry eye. With no prior use of prescription eyedrops, the patient began treatment with topical spironolactone ophthalmic solution, .005 mg/mL, four times a day OU.

Three months after beginning treatment with spironolactone ophthalmic solution, complaints of irritation resolved. The patient reported no irritation and improved intermittent sensation of dryness, as tear production normalized to 27 mm OD and 16 mm OS. Meibomian gland obstruction was decreased concurrent with improved appearance of the meibum turbidity. Unremarkable findings in the bulbar and palpebral conjunctiva and minimal fluorescein staining suggested a significant response to treatment. Intraocular pressure remained within normal limits at each visit, and corrected visual acuity remained constant at 20/25 OU.

Case 2

A patient in their 20s with a history of acute lymphocytic leukemia underwent HSCT in February 2019. Six months post-HSCT and immunosuppressive treatment with oral tacrolimus and prednisone, the patient complained of ocular discomfort and occasional blurring that resolved with blinking. Prior treatments only included artificial tear use. Tear film breakup time was measured at 5 seconds, while tear production was 23 mm OD and 25 mm OS, likely due to reflex tearing or tear film instability. Uncorrected vision was 20/20 OU. With no prior use of prescription ophthalmic drops, the patient began concurrent treatment with topical spironolactone ophthalmic solution, 0.005 mg/mL, and topical dapsone ophthalmic suspension, 2.5 mg/mL, twice a day.

One month later, the patient's complaints of discomfort resolved, with decreased frequency of blurring. The patient's V/O/T score was recorded as 0/2-3/4 OU, suggesting obstructive meibomian gland disease as a factor in the patient's complaints of discomfort. The patient's tear production measured at 5 mm OD and 8 mm OS at this visit. The patient's uncorrected vision remained stable at 20/20 OU.

Ten months post-HSCT, the patient showed extended improvement with prolonged use of spironolactone in his treatment. Tear production normalized to 12 mm OD and 21 mm OS, and frequency of blurring further decreased. Intraocular pressure remained within normal limits at each visit.

Case 3

A patient in their 30s with a history of mediastinal large cell lymphoma was diagnosed in June 2002 and treated with chemotherapy, HSCT, and total body irradiation by May 2003. Following a second HSCT in June 2019 and subsequent therapy with sirolimus, the patient was diagnosed in October 2019 with myelodysplastic syndrome.

In November 2019 the patient complained of extensive watering, blurriness, and soreness in the right eye. Uncorrected visual acuity was 20/30 OU. With tear production measured at 35 mm OD and 25 mm OS, V/O/T scores were recorded as 1/3 - 4/3 OU. The extensive obstruction and poor turbidity were suggestive of obstructive meibomian gland disease, a diagnosis of non-aqueous-deficient dry eye consistent with the Schirmer tear test findings. The patient began treatment with spironolactone ophthalmic solution, 0.005 mg/mL OU QID.

At 1-month follow-up, the patient showed marked improvement as reflected in symptomatology, visual acuity, and reduction in watering. The patient denied any ocular discomfort, consistent with decreased reflex tearing at 28 mm OD and 23 mm OS. Visual acuity improved to 20/20 OU. V/O/T scores were recorded as 1/3/2 OD and 1/3 - 4/3 OS, suggesting improved meibum quality and correspondingly decreased evaporative tear film loss from the right eye. Intraocular pressures remained stable and within normal limits at each visit.

Discussion and Conclusion

Both aGVHD and cGVHD involve host tissue destruction mediated by donor T lymphocytes. Infiltration and cytotoxic effects of CD8+ cells have been implicated in the degenerative cutaneous changes associated with cGVHD [29-32]. While the progression of aGVHD can be described in stages, damage to the skin, GI tract and liver are usually caused by both cytotoxic T lymphocytes and proinflammatory cytokines released by various lymphocytes [9,33].

Pathogenesis of the various factors that may contribute to the secondary sicca associated with ocular GVHD remains poorly understood. Ocular symptoms of GVHD may be present with or without systemic manifestation of GVHD, but diagnosis of ocular keratoconjunctivitis sicca due to GVHD is complicated by the possibility of underlying dry eye disease prior to onset of GVHD. Early detection of signs and symptoms of ocular GVHD may better guide management of both the secondary sicca and degenerative changes associated with the disease process.

The development and resolution of ocular GVHD has been described by Kiang., *et al*. [12] in 1998 as a four-stage process: subclinical, active, necrotizing and convalescent. The cases described in this brief report ranged between the active and convalescent stages, with clinical improvement of blurring, epithelial staining, reflex tearing, conjunctival inflammation and meibomian gland disease noted with concurrent use of spironolactone ophthalmic solution, particularly in cases of non-aqueous dry eye.

These cases highlight the importance of managing ocular GVHD signs and symptoms by improving meibomian gland oil secretions to re-establish a protective lipid layer. Spironolactone is a synthetic 17-lactone steroid with both anti-androgenic and anti-inflammatory properties, in addition to its anti-hypertensive effect [27]. Its anti-androgenic effect is due to a number of mechanisms, including regulating androgen receptors with a weak partial agonist effect, inhibiting key enzymes (17α-hydroxylase) in the androgen biosynthetic pathway, activating the progesterone receptor and inhibiting of 5α-reductase, a key enzyme in the synthesis of dihydrotestosterone (DHT), a potent androgen [22]. Because of the influence of androgens on lipid secretion [34], it is plausible that spironolactone may improve the quality of meibomian gland secretions and affect the treatment of dry eye and meibomian gland dysfunction. Topical administration of spironolactone ophthalmic solution has been shown to improve symptoms and signs of dry eye patients who failed with commercially available prescribed dry eye treatments over a 2 - 4 week period [35,36]. While the mechanism(s) is not known specifically in dry eye disease, *in vitro* experiments confirm the presence of mRNA transcripts of the ELOVL4 gene in both primary and immortalized corneal epithelial cells treated with spironolactone [37]. The ELOVL4 gene has been demonstrated in meibomian glands and modulates long chain fatty acid synthesis [38]. *In vitro* human corneal epithelial cell studies have also shown that spironolactone ophthalmic solution has a stimulatory effect on lipid secretion in primary and immortalized corneal epithelial cells and promotes lipid production as evidenced by O red O staining [24-26]. Notably, spironolactone has also shown several mineralocorticoid receptor-independent effects since its anti-androgenic properties have been elucidated. Such effects include *in vitro* immunomodulation via inhibition of cytokine produc-

tion in mononuclear cells, anti-NF-κB signalling cascade activity, and even inhibition of viral lytic cycle activity [39,40]. While specific mechanisms remain unknown, these properties of spironolactone suggest that spironolactone may affect several signaling pathways to ultimately promote stabilization of the ocular surface in cases of ocular GvHD.

Literature documents the relationships between spironolactone and lipid synthesis, transport, and immunomodulation. Taken together, these pharmacological properties suggest that spironolactone ophthalmic solution has therapeutic efficacy in diseases of impaired ocular surface and dry eye. Future prospective, controlled studies would be beneficial for an understanding of effective, multifactorial treatment of both non-aqueous and aqueous aspects of dry eye associated with oGVHD. Such studies are also needed to further validate the effect of spironolactone ophthalmic solution in dry eye associated with HSCT and oGVHD.

Conflicts of Interest

Two authors declare no conflicts of interest. R W Yee owns a patent for topical spironolactone.

Bibliography

1. Qiu Y., *et al*. "Manifestation of Clinical Categories of Ocular Graft-versus-Host Disease". *Journal of Ophthalmology* (2018): 6430953.
2. Ocular Graft-versus-Host Disease: A Review | Elsevier Enhanced Reader.
3. Ocular findings and ocular graft-versus-host disease after allogeneic stem cell transplantation without total body irradiation | Bone Marrow Transplantation (2020).
4. Nassar A., *et al*. "Ocular manifestations of graft-versus-host disease". *Saudi Journal of Ophthalmology* 27.3 (2013): 215-222.
5. Munir SZ and Aylward J. "A Review of Ocular Graft-Versus-Host Disease". *Optometry and Vision Science* 94.5 (2017): 545-555.
6. Sullivan KM. "Acute and chronic graft-versus-host disease in man". *The International Journal of Cell Cloning* 4.1 (1986): 42-93.
7. Sullivan KM., *et al*. "Chronic graft-versus-host disease in 52 patients: adverse natural course and successful treatment with combination immunosuppression". B*lood* 57.2 (1981): 267-276.
8. Atkinson K. "Chronic graft-versus-host disease". *Bone Marrow Transplant* 5.2 (1990): 69-82.
9. Goker H., *et al*. "Acute graft-vs-host disease: pathobiology and management". *Experimental Hematology* 29.3 (2001): 259-277.
10. Lawley TJ., *et al*. "Scleroderma, Sjögren-like syndrome, and chronic graft-versus-host disease". *Annals of Internal Medicine* 87.6 (1977): 707-709.
11. Gratwhol AA. "Sjögren-Type Syndrome After Allogeneic Bone-Marrow Transplantation". *Annals of Internal Medicine* 87.6 (1977): 703.
12. Kiang E., *et al*. "The use of topical cyclosporin A in ocular graft-versus-host-disease". *Bone Marrow Transplant* 22.2 (1998): 147-151.
13. Hirst LW., *et al*. "The eye in bone marrow transplantation. I. Clinical study". *Archives of Ophthalmology* 101.4 (1983): 580-584.
14. Franklin RM., *et al*. "Ocular manifestations of graft-vs-host disease". *Ophthalmology* 90.1 (1983): 4-13.
15. Late-onset Keratoconjunctivitis Sicca Syndrome After Bone Marrow Transplantation: Incidence and Risk Factors. European Group or Blood and Marrow Transplantation (EBMT) Working Party on Late Effects (2020).
16. The Eye in Bone Marrow Transplantation. III. Conjunctival Graft-Vs-Host Disease (2020).

17. Jabs DA., *et al*. "The Eye in Bone Marrow Transplantation: II. Histopathology". *Archives of Ophthalmology* 101.4 (1983): 585-590.

18. Livesey SJ., *et al*. "Ocular complications of bone marrow transplantation". *Eye* 3.3 (1989): 271-276.

19. Tuchocka-Piotrowska A., *et al*. "[Graft-versus-host disease as the cause of symptoms mimicking Sjögren's syndrome]". *Annales Academiae Medicae Stetinensis* 52.2 (2006): 89-93.

20. Jack MK., *et al*. "Ocular manifestations of graft-v-host disease". *Archives of Ophthalmology* 101.7 (1983): 1080-1084.

21. Ogawa Y., *et al*. "International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: Proposed Diagnostic Criteria for Chronic GVHD (Part I)". *Scientific Reports* (2013): 3.

22. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease – Science Direct (2020).

23. Prabhasawat P., *et al*. "A Randomized Double-Masked Study of 0.05% Cyclosporine Ophthalmic Emulsion in the Treatment of Meibomian Gland Dysfunction". *Cornea* 31.12 (2012): 1386-1393.

24. Comparison of Autologous Serum Eye Drops with Different Diluents: Current Eye Research: 38.1 (2020).

25. Na K-S and Kim MS. "Allogeneic serum eye drops for the treatment of dry eye patients with chronic graft-versus-host disease". *Journal of Ocular Pharmacology and Therapeutics* 28.5 (2012): 479-483.

26. Foulks GN., *et al*. "Topical azithromycin and oral doxycycline therapy of meibomian gland dysfunction: a comparative clinical and spectroscopic pilot study". *Cornea* 32.1 (2013): 44-53.

27. Fagart J., *et al*. "A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule". *Journal of Biological Chemistry* 285.39 (2010): 29932-29940.

28. Arita R., *et al*. "MGD Diagnosis". *Current Ophthalmology Reports* 2.2 (2014): 49-57.

29. Bhan AK., *et al*. "T-cell subsets and Langerhans cells in normal and diseased conjunctiva". *American Journal of Ophthalmology* 94.2 (1982): 205-212.

30. Kaye VN., *et al*. "Identity of immune cells in graft-versus-host disease of the skin. Analysis using monoclonal antibodies by indirect immunofluorescence". *The American Journal of Pathology* 116.3 (1984): 436-440.

31. Takata M. "Immunohistochemical identification of perforin-positive cytotoxic lymphocytesin graft-versus-host disease". *American Journal of Clinical Pathology* 103.3 (1995): 324-329.

32. Immunoelectron microscopy of acute graft versus host disease of the skin after allogeneic bone marrow transplantation (2020).

33. Ferrara JL., *et al*. "Evidence that large granular lymphocytes of donor origin mediate acute graft-versus-host disease". *Transplantation* 47.1 (1989): 50-54.

34. Imperato-McGinley J., *et al*. "The androgen control of sebum production. Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity". *The Journal of Clinical Endocrinology and Metabolism* 76.2 (1993): 524-528.

35. Johnson JR., *et al*. "Topical Spironolactone in the Treatment of Meibomian Gland Dysfunction". *Investigative Ophthalmology and Visual Science* 58.8 (2017): 2249-2249.

36. Yee RW., *et al*. "Topical spironolactone in the treatment of meibomian gland dysfunction". *Investigative Ophthalmology and Visual Science* 57.12 (2016): 5664-5664.

37. Watsky M. Work in preparation.

38. Cadieux-Dion M., *et al*. "Expanding the Clinical Phenotype Associated with ELOVL4 Mutation: Study of a Large French-Canadian Family With Autosomal Dominant Spinocerebellar Ataxia and Erythrokeratodermia". *JAMA Neurology* 71.4 (2014): 470-475.

39. Sønder SUS., *et al*. "Effects of spironolactone on human blood mononuclear cells: mineralocorticoid receptor independent effects on gene expression and late apoptosis induction". *British Journal of Pharmacology* 148.1 (2006): 46-53.

40. Verma D., *et al*. "Spironolactone blocks Epstein–Barr virus production by inhibiting EBV SM protein function". *Proceedings of the National Academy of Sciences of the United States of America* 113.13 (2016): 3609-3614.

Volume 12 Issue 7 July 2021