Review Article

Management of Ocular Graft-Versus-Host Disease: A Brief Review

Melika Samadi [1], MD; Mohammad Soleimani [1,*], MD

1- Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran.

***Corresponding author:** Mohammad Soleimani
E-mail: soleimani_md@yahoo.com

Abstract

Graft-versus-host disease (GVHD) remains a major complication following hematopoietic stem cell transplantation (HSCT). Ocular GVHD develops in a substantial number of patients following HSCT and 60 % to 90 % of patients with systemic GVHD experience the ocular complications to some extents. In this brief review we will discuss the conventional and updated novel therapies in the management of patients suffering from ocular GVHD.

Keywords: Eye; Dry Eye; Graft Versus Host Disease; Treatment.

Article Notes: Received: Jun 1, 2019; Received in revised form: Jul. 7, 2019; Accepted: Jul. 27, 2019; Available Online: Oct. 1, 2019.

How to cite this article: Melika Samadi M, Mohammad Soleimani M. Management of Ocular Graft-Versus-Host Disease: A Brief Review. Journal of Ophthalmic and Optometric Sciences . 2019;3(4): 51-7.

Introduction

Graft-versus-host disease (GVHD) remains a major complication following hematopoietic stem cell transplantation (HSCT) due to donor derived immune interactions against the host antigens and consequent non-relapse associated morbidity and mortality [1]. GVHD occurs in 10 % to 90 % of patients with HSCT with various probable risk factors related to the patients' characteristics including age, ethnicity and sex, source of the of donor stem cells and pre-transplant medical conditions [2,3].

Acute GVHD was traditionally referred to any alloimmunity manifestations developing within the first 100 days after transplantation; conversely, the chronic GVHD was referred to any reaction after this time [4]. However, according to the new National Institute of Health (NIH) classification, distinct clinical signs and symptoms differentiate acute and chronic GVHD [5]. Acute GVHD is now referred to an immediate inflammatory response involving multiple organs including skin, digestive system and liver, while chronic GVHD is characterized by multi-organ inflammation and fibrosis affecting skin, eyes, gastrointestinal tract and lungs. The complex features of fibrosis and inflammation in chronic GVHD mimic the manifestations of collagen vascular diseases [6].

Ocular GVHD develops in a substantial number of patients following HSCT and 60 % to 90 % of patients with systemic GVHD experience the ocular complications to some extents [7]. The diagnostic criteria for ocular GVHD, updated recently by NIH, refer to the recent onset of dry eye manifestations as well as cicatricial keratoconjunctivitis [8–10]. New specialized diagnostic criteria have been proposed recently by the International Consensus Group which contains subjective and objective parameters to be administered by ophthalmologists in monitoring the patients. Conjunctival hyperemia, Schirmer's test, corneal staining and ocular discomfort symptoms are the aforementioned parameters [11].

In this brief review we will focus on the conventional and updated novel therapies in the management of patients suffering from ocular GVHD.

Medical Management

The therapeutic priority in patients with ocular GVHD is given to topical medical managements, however surgical and systemic options may be required in severe cases. According to the NIH consensus workshop on GVHD, lubrication, control of tear drainage and evaporation and reducing the ocular surface inflammation are the recommended mainstays of treatment in ocular GVHD. These recommendations are mainly aimed at decreasing the dry eye signs and discomfort by improving the tear function and reducing the inflammation [12].

Frequent instilling of the non-preservative artificial tear substitutes is the first and the most required treatment in these patients to lubricate the ocular surface and to dilute the inflammatory cytokines [13–15]. The most tolerable brand should be found for each individual patient, however phosphate enriched products should be avoided to prevent crystalline deposit formation on inflamed ocular surface [16].

To maintain tear stability, the drainage system should be occluded by temporary punctual plugs or permanent thermal cauterization. In spite of presumably inflammatory cytokine accumulation within the eye following punctual occlusion, which might be worrisome in such inflamed eyes, a recent study has demonstrated

no significant adverse effect of this treatment in aggravating inflammation [17]. On the other hand, another strategy to support tear stability is to prevent evaporation by supplying the optimal lipid layer thickness. Improving eyelid hygiene with warm compress and digital massage effectively help meibomian glands function and reduce tear film evaporation [18]. Systemic tetracycline products as well as topical ointments have some benefits in poorly responsive patients to liquefy lipid products and facilitate their secretion [19]. Brimonidine eye drop, an α2 adrenergic agonist, has been shown to improve meibomian gland epithelialization and ameliorate dry eye signs and symptoms [20]. Omega-3 fatty acid supplementations also might alleviate dry eye symptoms by improving meibomian gland function [21].

To control the ocular surface inflammation the first line therapeutic option are topical corticosteroids; although their long-term adverse effects are not favorable especially in such inflamed compromised eyes [22]. So it has been suggested to use steroids in short-time induction pulse therapy with close monitoring and bridge it with topical immunosuppression therapy with cyclosporine or tacrolimus .Topical cyclosporine is an alternative anti-inflammatory drug which has been reported to control inflammation in ocular GVHD as much as corticosteroids [23]. Also the prophylactic administration of cyclosporine 0.05 % prior to HSCT has been reported to be beneficial in decreasing the incidence and severity of ocular GVHD. It should be started a month prior to transplantation to play a prophylactic role [24]. Subconjunctival cyclosporine implant has been also introduced recently to bypass the epithelial surface and increase the concentration of the drug adjacent to the lacrimal gland. Topical tacrolimus is another alternative to lessen the localized inflammation without the aforementioned adverse effects of steroids [25]. Topical vitamin A is also helpful in controlling the dry eye symptoms, which is comparable to cyclosporine 0.05 % efficacy [26]. Blood-derived eye drops have been demonstrated to improve dry eye signs and symptoms with 80 % success rate [27]. Lacrimal gland infiltration and fibrosis lead to aqueous tear deficiency dry eye following ocular GVHD, which decreases the quality and quantity of tear film secretion. The biologic eye drops help to protect and nourish the irritated corneal epithelium in these patients [28]. Administering the biologic agents earlier in the course of the disease and in milder cases has been encouraged recently. Diluted autologous serum is much more common with balanced amounts of inflammatory cytokines; but non-diluted eye drops have also been administered without adverse effects with similar efficacy [29]. However, in patients with severe GVHD the use of autologous serum is worrisome due to excessive amount of systemic pro-inflammatory cytokines which could be detrimental for the ocular surface; hence the use of allogeneic serum of healthy donors or cord blood serum eye drops are better substitutes [30,31].

Administering hard or soft scleral contact lenses may provide additional corneal protection, minimize the bothersome ocular surface discomfort and improve the visual function, leading to increase patients' satisfaction. The contact lens also protects the ocular surface from further trauma of eyelids and masks the corneal irregularities [32].

Surgical management

Patients with GVHD are prone to persistent epithelial defects and corneal perforation.

Partial tarsorrhaphy decreases tear evaporation and it is a beneficial surgical treatment which should be considered as early as possible along with other therapeutic options [33]. Amniotic membrane transplantation (AMT) promotes epithelialization and controls inflammation, so it is useful in improving corneal persistent epithelial defects [34]. Multilayer AMT can also be used in small corneal perforations; however cases with corneal melting and perforation are offered to undergo tectonic keratoplasty to keep the eye's integrity despite its poor prognosis [35].

The compromised ocular surface of patients with GVHD has been originated from the stem cell, goblet cell and mucin deficiency and theoretically it would be better to perform limbal stem cell and conjunctival transplantation in severe cases. Allogeneic limbal stem cell transplantation with in vitro amplification of epithelial progenitor cells is preferred in such patients due to severe bilateral limbal stem cell deficiency. However allogenicity may lead to another immunologic rejection and require systemic immunosuppression therapy [36]. To prevent rejection, it has been suggested to extract the progenitor limbal cells from the same bone marrow donor due to the previously acquired tolerance during the bone marrow transplantation. In this method no systemic immunosuppression therapy is required and further conjunctival transplantation from the primary bone marrow donor can also be performed to alleviate the dry eye signs and symptoms [37,38].

Any elective surgery in patients with chronic GVHD including cataract surgery should be performed after sufficient control of the ocular inflammation and dry eye signs and symptoms, since worsening of symptoms has been reported following cataract surgery [33].

Discussion

The therapeutic priority in patients with GVHD is given to topical medical managements, however surgical and systemic options may be required in severe cases. Lubrication, control of tear drainage and evaporation and reducing the ocular surface inflammation are the recommended mainstays of treatment in ocular GVHD. These recommendations are mainly aimed at decreasing the dry eye signs and discomforts by improving the tear function and reducing the inflammation [12]. After sufficient medical management and surgical procedures to improve the condition of the ocular surface in highly inflamed eyes and when the inflammation gets resolved to some extent, more surgical interactions could be performed to better control the disease.

Elective surgeries in patients with chronic GVHD including cataract surgery should be performed after controlling the ocular inflammation and dry eye signs and symptoms, since a worsening of symptoms might occur following these surgeries [33].

To maximize the objective and subjective response, the patients must be educated to not only fully follow their treatment but also refine their environment. Humidifying the room and balancing the temperature are among the environmental managements.

Conclusion

Ocular GVHD develops in a substantial number of patients following HSCT. Although several medical and surgical treatments have been suggested for treating ocular GVHD improving the current medications as well as development of novel therapeutic options will help in reducing the burden of ocular GVHD.

Authors ORCIDs

Melika Samadi:
https://orcid.org/0000-0001-8087-1452
Mohammad Soleimani:
https://orcid.org/0000-0002-6546-3546

References

1. Milosevic S, Bachnick B, Karim K, Bornkamm GW, Witter K, Gerbitz A, et al. Identification of MHC II-restricted minor histocompatibility antigens after HLA-identical stem-cell transplantation. Transplantation. 2010;90(9):1030-5.
2. Vigorito AC, Azevedo WM, Marques JF, Azevedo AM, Eid KA, Aranha FJ, et al. A randomised, prospective comparison of allogeneic bone marrow and peripheral blood progenitor cell transplantation in the treatment of haematological malignancies. Bone Marrow Transplant. 1998;22(12):1145-51.
3. Jagasia M, Arora M, Flowers ME, Chao NJ, McCarthy PL, Cutler CS, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood. 2012;119(1):296-307.
4. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med. 1980;69(2):204-17.
5. Pavletic SZ, Vogelsang GB, Lee SJ. 2014 National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: preface to the series. Biol Blood Marrow Transplant. 2015;21(3):387-8.
6. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550-61.
7. Jacobs R, Tran U, Chen H, Kassim A, Engelhardt BG, Greer JP, et al. Prevalence and risk factors associated with development of ocular GVHD defined by NIH consensus criteria. Bone Marrow Transplant. 2012;47(11):1470-3.
8. Dietrich-Ntoukas T, Cursiefen C, Westekemper H, Eberwein P, Reinhard T, Bertz H, et al. Diagnosis and treatment of ocular chronic graft-versus-host disease: report from the German-Austrian-Swiss Consensus Conference on Clinical Practice in chronic GVHD. Cornea. 2012;31(3):299-310.
9. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. 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(12):945-56.
10. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015;21(3):389-401.e1.
11. Ogawa Y, Kim SK, Dana R, Clayton J, Jain S, Rosenblatt MI, et al. International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: proposed diagnostic criteria for chronic GVHD (Part I). Sci Rep. 2013;3:3419.
12. Carpenter PA, Kitko CL, Elad S, Flowers ME, Gea-Banacloche JC, Halter JP, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transplant. 2015;21(7):1167-87.
13. Nassiri N, Eslani M, Panahi N, Mehravaran

S, Ziaei A, Djalilian AR. Ocular graft versus host disease following allogeneic stem cell transplantation: a review of current knowledge and recommendations. J Ophthalmic Vis Res. 2013;8(4):351-8.
14. Jabs DA, Hirst LW, Green WR, Tutschka PJ, Santos GW, Beschorner WE. The eye in bone marrow transplantation. II. Histopathology. Arch Ophthalmol. 1983;101(4):585-90.
15. Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. Surv Ophthalmol. 2013;58(3):233-51.
16. Doughty MJ, Glavin S. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. Ophthalmic Physiol Opt. 2009;29(6):573-83.
17. Sabti S, Halter JP, Braun Fränkl BC, Goldblum D. Punctal occlusion is safe and efficient for the treatment of keratoconjunctivitis sicca in patients with ocular GvHD. Bone Marrow Transplant. 2012;47(7):981-4.
18. Yin Y, Gong L. Reversibility of Gland Dropout and Significance of Eyelid Hygiene Treatment in Meibomian Gland Dysfunction. Cornea. 2017;36(3):332-7.
19. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, et al. 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(4):2050-64.
20. Han X, Liu Y, Kam WR, Sullivan DA. Effect of brimonidine, an α2 adrenergic agonist, on human meibomian gland epithelial cells. Exp Eye Res. 2018;170:20-8.
21. Giannaccare G, Pellegrini M, Sebastiani S, Bernabei F, Roda M, Taroni L, et al. Efficacy of Omega-3 Fatty Acid Supplementation for Treatment of Dry Eye Disease: A Meta-Analysis of Randomized Clinical Trials. Cornea. 2019;38(5):565-73.
22. Inamoto Y, Petriček I, Burns L, Chhabra S, DeFilipp Z, Hematti P, et al. Non-GVHD ocular complications 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(5):648-61.
23. Wang Y, Ogawa Y, Dogru M, Kawai M, Tatematsu Y, Uchino M, et al. Ocular surface and tear functions after topical cyclosporine treatment in dry eye patients with chronic graft-versus-host disease. Bone Marrow Transplant. 2008;41(3):293-302.
24. Boynton GE, Raoof D, Niziol LM, Hussain M, Mian SI. Prospective Randomized Trial Comparing Efficacy of Topical Loteprednol Etabonate 0.5 % Versus Cyclosporine-A 0.05 % for Treatment of Dry Eye Syndrome Following Hematopoietic Stem Cell Transplantation. Cornea. 2015;34(7):725-32.
25. Abud TB, Amparo F, Saboo US, Di Zazzo A, Dohlman TH, Ciolino JB, et al. A Clinical Trial Comparing the Safety and Efficacy of Topical Tacrolimus versus Methylprednisolone in Ocular Graft-versus-Host Disease. Ophthalmology. 2016;123(7):1449-57.
26. Kim EC, Choi JS, Joo CK. A comparison of vitamin a and cyclosporine a 0.05 % eye drops for treatment of dry eye syndrome. Am J Ophthalmol. 2009;147(2):206-13.e3.
27. Pezzotta S, Del Fante C, Scudeller L, Cervio M, Antoniazzi ER, Perotti C. Autologous platelet lysate for treatment of refractory ocular GVHD. Bone Marrow Transplant. 2012;47(12):1558-63.
28. Giannaccare G, Versura P, Buzzi M, Primavera L, Pellegrini M, Campos EC. Blood derived eye drops for the treatment of cornea and ocular surface diseases. Transfus Apher Sci. 2017;56(4):595-604.

29. Tahmaz V, Gehlsen U, Sauerbier L, Holtick U, Engel L, Radojska S, et al. Treatment of severe chronic ocular graft-versus-host disease using 100 % autologous serum eye drops from a sealed manufacturing system: a retrospective cohort study. Br J Ophthalmol. 2017;101(3):322-6.
30. 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(7):861-3.
31. Buzzi M, Versura P, Grigolo B, Cavallo C, Terzi A, Pellegrini M, et al. Comparison of growth factor and interleukin content of adult peripheral blood and cord blood serum eye drops for cornea and ocular surface diseases. Transfus Apher Sci. 2018;57(4):549-55.
32. Takahide K, Parker PM, Wu M, Hwang WY, Carpenter PA, Moravec C, et al. Use of fluid-ventilated, gas-permeable scleral lens for management of severe keratoconjunctivitis sicca secondary to chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2007;13(9):1016-21.
33. Hessen M, Akpek EK. Ocular graft-versus-host disease. Curr Opin Allergy Clin Immunol. 2012;12(5):540-7.
34. Peric Z, Skegro I, Durakovic N, Desnica L, Pulanic D, Serventi-Seiwerth R, et al. Amniotic membrane transplantation-a new approach to crossing the HLA barriers in the treatment of refractory ocular graft-versus-host disease. Bone Marrow Transplant. 2018;53(11):1466-9.
35. Di Zazzo A, Kheirkhah A, Abud TB, Goyal S, Dana R. Management of high-risk corneal transplantation. Surv Ophthalmol. 2017;62(6):816-27.
36. Holland EJ, Mogilishetty G, Skeens HM, Hair DB, Neff KD, Biber JM, et al. Systemic immunosuppression in ocular surface stem cell transplantation: results of a 10-year experience. Cornea. 2012;31(6):655-61.
37. Starzl TE, Demetris AJ. Transplantation tolerance, microchimerism, and the two-way paradigm. Theor Med Bioeth. 1998;19(5):441-55.
38. Busin M, Giannaccare G, Sapigni L, Testoni N, Leon P, Versura P, et al. Conjunctival and Limbal Transplantation From the Same Living-Related Bone Marrow Donor to Patients With Severe Ocular Graft-vs-Host Disease. JAMA Ophthalmol. 2017;135(10):1123-5.

Footnotes and Financial Disclosures

Conflict of interest

The authors have no conflict of interest with the subject matter of the present manuscript.