International Medical Society
http://imedicalsociety.org

International Archives of Medicine
Section: Ophtalmology
ISSN: 1755-7682

2016
Vol. 9 No. 53
doi: 10.3823/1924

Evidence for Dry Eye Treatment in Hematopoietic Stem Cells Post-Transplantation

REVIEW

Isabelle Campos de Azevedo[1], Jéssica Naiara de Medeiros Araújo[1], Isabelle Katherinne Fernandes Costa[1], Alexsandra Rodrigues Feijão[1], Rita de Cássia Lira da Silva[1], Jéssica de Araújo Olímpio[1], Priscila Fernandes Meireles Câmara[1], Hanna Priscila da Silva[1], Jéssica Valeska Herculano Lima[1], Danielly Oliveira Pitombeira[1], Allyne Fortes Vitor[1], Marcos Antonio Ferreira Júnior[1]

1 Departamento de Enfermagem, Universidade Federal do Rio Grande do Norte, Natal/RN, Brasil.

Contact information:

Isabelle Campos de Azevedo.
Universidade Federal do Rio Grande do Norte, Centro de Ciências da Saúde, Departamento de Enfermagem.

Address: Avenida Salgado Filho, S/N, Lagoa Nova, Natal, RN, Brasil. CEP: 59078970.

isabellebr2511@gmail.com

Abstract

Introduction: Hematopoietic Stem Cell Transplantation (HSCT) is a treatment modality for oncology and hematological diseases genetically inherited or acquired. The morbidities and mortalities related to HSCT are evident in its different phases, such as the Graft Versus Host Disease especially on dry eye syndrome, one of the most complication of chronic phase, characterized as a multifactorial disease of the ocular surface. Several treatments may be directed to the dry eye and the consequences caused by it during the HSCT post-period.

Objective: To reveal the treatments for dry eye in patients after HSCT period.

Method: This is a literature integrative review performed by the SCOPUS databases, National Library of Medicine (PubMed); Web of Science and Cumulative Index to Nursing and Allied Heath Literature (CINAHL).

Results: Of the 1,551 articles identified, there were 21 in the final sample. Regarding the treatments addressed, the most often used was found the cyclosporine 0.05%, followed by allogeneic and autologous drops.

Conclusion: There was no consensus identified as the best type of treatment for these patients. However, it is known that depend mainly on clinical features of chronic graft-versus-host eye on the post-transplantation situation.

Keywords
Hematopoietic Stem Cell Transplantation; Bone Marrow Transplantation; Graft vs. host disease; Keratoconjunctivitis Sicca; Dry Eye Syndromes.

Introduction

The Hematopoietic Stem Cell Transplantation (HSCT) is a treatment modality used more frequently for oncology and hematological diseases genetically inherited or acquired [1-2]. The HSCT may occur by autologous transplantation, when Hematopoietic Progenitor Cells (HPC) are from the patient; allogeneic when HPC come from donors with compatible Human Leukocyte Antigen (HLA), related when they are of the same family and not related if it is not from an inbred donor; or syngeneic transplantation, when HPC are from identical twins [3].

The morbidities and mortalities related to HSCT are expressive in its different phases, from pre-transplantation and conditioning until the stage of post-transplantation recovery, in which these risks are magnified [2]. The graft-versus-host disease (GVHD) is presented as the main complication after HSCT, more frequently in allogeneic transplantations [1-3]. This can affect many organ systems and cause consequences to transplant patients, both in an acute form, in the first 100 days after HSCT as in the chronic form after this period [4].

One of the main complications of GVHD chronic phase is the dry eye syndrome, characterized by a multifactorial disease of the ocular surface that results in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface resulting mucin dysfunction [5] of immune-mediated inflammation and fibrosis [6].

Dry eye syndrome is divided into two phases, which mechanisms include irritating environmental stimuli to ocular tissues during the first phase; and developments neuropathic, metabolic or inflammatory in the second phase with the consequent instability of the tear film, decreased tear secretion and increased evaporation or change in the composition of the tear [7-8].

Several treatments may be directed to the dry eye, to problems and complications caused by it during the HSCT post-period. Thus, it was decided to carry out an integrative literature review to highlight the treatments for dry eye in patients after HSCT period to support discussions on the subject.

Method

It is an integrative literature review defined as a specific method to synthesize and evaluate evidence available in the literature to provide a greater understanding of specific research problem [9-10].

The following steps were created to check the critical scientific review: identification of the problem or research question; literature search, with inclusion of the definition of inclusion and exclusion criteria of the articles; evaluation of data for defining the information to be extracted from selected articles; critical analysis of selected studies and the presentation of the review [10].

In the origin of the study there was the following question: What are the treatments for dry eye in patients in transplantation of hematopoietic stem cells post-period?

The search in the databases occurred in June 2015, conducted by peers using proxy licensed by the Federal University of Rio Grande do Norte/Brazil (www.capes.ufrn.br/porta 3128) on different machines, at the same time and same network internet through the access to the following databases: SCOPUS, National Library of Medicine (PubMed); Web of Science and Cumulative Index to Nursing and Allied Heath Literature (CINAHL).

To search databases, the following keywords and their synonyms were used, identified in the Medical Subject Headings (MeSH): 1# (Hematopoietic Stem Cell Transplantation OR Transplantation, Hematopoietic Stem Cell OR Stem Cell Transplantation, Hematopoietic); 2# (Bone Marrow Transplantation OR Transplantation, Bone Marrow OR Grafting, Bone Marrow OR Bone Marrow Grafting OR Bone Marrow Cell Transplantation OR Transplantation, Bone Marrow Cell); 3# (Dry Eye Syndromes OR Dry Eye Syndrome OR Syndrome, Dry Eye OR Syndromes, Dry Eye); 4# (Therapeutics OR Therapeutic OR

Treatment OR Treatments OR Therapy OR Therapies). The crosses were performed with the use of Boolean operator as 1# AND 3# AND 4# and 2# AND 3# AND 4#.

Each database carried out a not controlled search to identify studies that by indexing differences would not be located using the controlled descriptor.

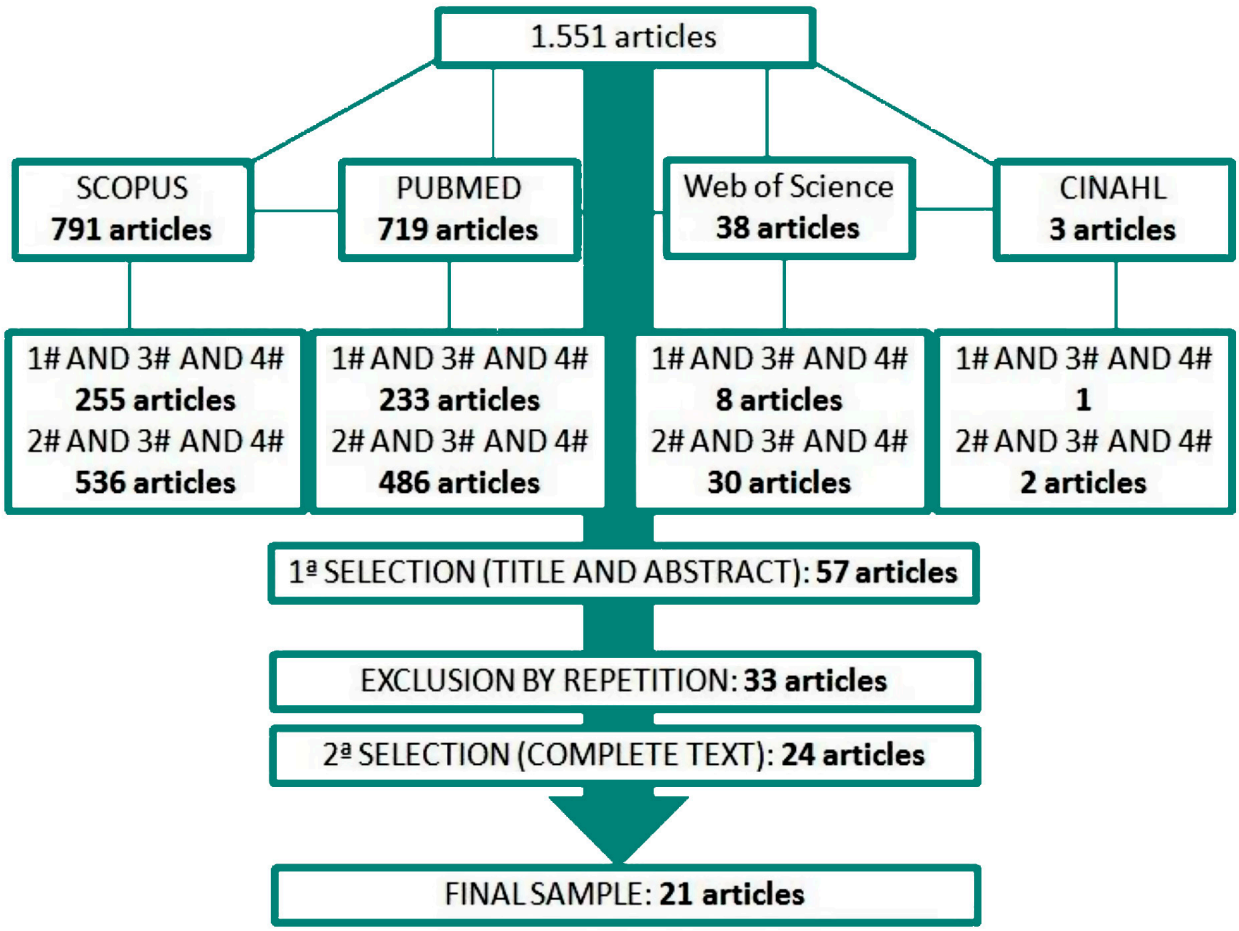
For a selection of the studies, the following inclusion criteria were used: full articles available on selected databases and articles addressing treatments for dry eye in patients of post-transplantation hematopoietic stem cells/bone marrow transplantation. Editorials, letters to the editor, abstracts, expert opinion, reviews, books, book chapters, theses, and dissertations were excluded.

After the search, studies were pre-selected with a careful reading of the titles and abstracts to identify the relationship with the guiding question of the review and the adopted inclusion and exclusion criteria. Then, the reading of the pre-selected items was held in full by a pair of independent reviewers. Disagreements between reviewers were resolved by consensus or by the opinion of a third reviewer [11-12].

For the analysis and data extraction, a script that contains the following information was developed and used: a publication of the identification, location of the study, methodological aspects, adopted treatment, conclusions/limitations of the research [13]. The strategy used for critical evaluation of the studies was to identify the level of evidence and grade of recommendation. Articles were classified according to the level of evidence, to consider the research design of each study [14].

The electronic search process of studies in the databases resulted in 1,551 articles, of which 21

Figure 1: Synthesis of the studies selection process.



were selected to compose the review sample. The articles repeated in the database were excluded, as shown in **Figure 1**.

After reading the articles in full, the data have been described and presented in a **table 1** and **figure 2**.

Figure 2: The frequency of the types of treatment used in the studies. *Punctual cauterization, anakinra 2.5% autologous serum, Boston contact lenses.

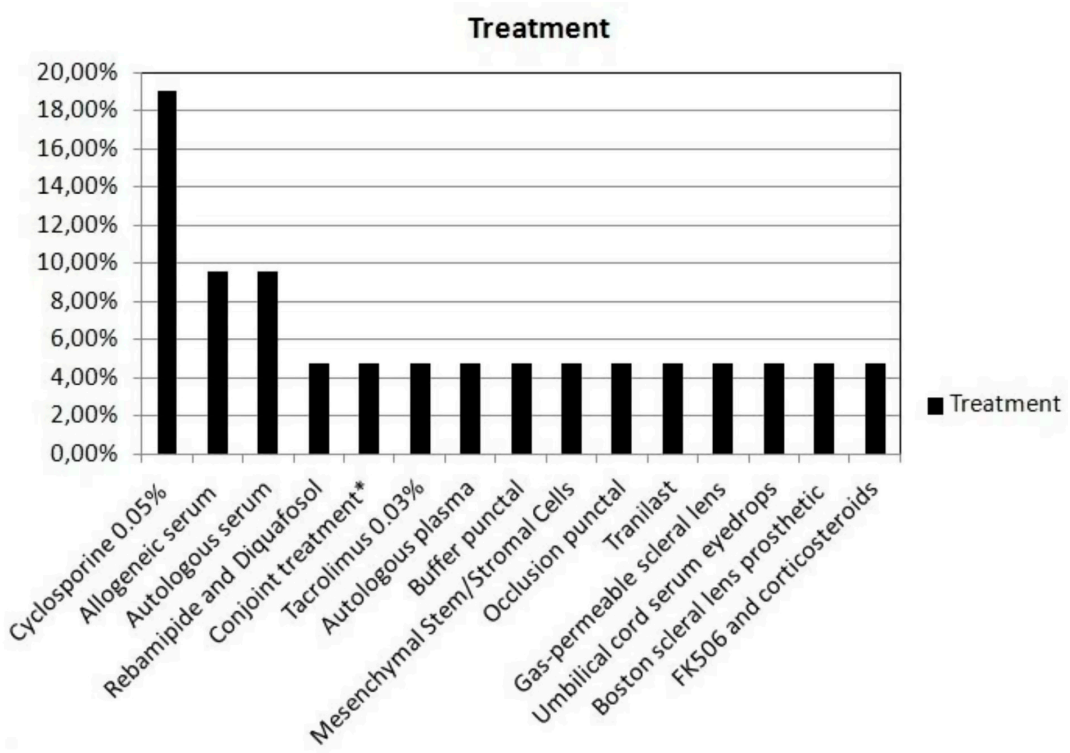


Table 1. Characterization of the articles according to year, reference/database, place/language and method/level of evidence/grade of recommendation. Natal, 2016 (n = 21).

Year	Author/Database	Country/ Language	Méthod/Evidênce Level/Degree of Recommendation
2003	- Ogawa Y, Okamoto S, Mori T, Yamada M, Mashima Y, Watanabe R. et al. [15] - Scopus	- Japan - English	- Clinical essay study - Evidence II - Moderate degree
2012	- Pezzotta S, Fante CD, Scudeller L, Cervio M, Antoniazzi ER, Perotti C. [16] - Scopus/Web of Science	- Italy - English	- Clinical essay study - Evidence III - Moderate degree
2012	- Weng J, He C, Lai P, Luo C, Guo R, Wu S. et al. [17] - Scopus/Pubmed	- China - English	- Clinical essay study - Evidence III - Moderate degree
2010	- Ogawa Y, Dogru M, Uchino M, Tatematsu Y, Kamoi m, Yamamoto Y. et al. [6] - Scopus	- Japan - English	- Clinical essay study - Evidence III - Moderate degree
2008	- Wang Y, Ogawa Y, Dogru M, Kawai M, Tatematsu Y, Uchino M. et al. [18] - Scopus/Web of Science	- Japan - English	- Clinical essay study - Evidence III - Moderate degree

Year	Author/Database	Country/ Language	Méthod/Evidênce Level/Degree of Recommendation
2007	- Yoon KC, Jeong IY, Im SK, Park YG, Kim HJ, Choi J. [19] - Scopus	- South Korea - English	- Clinical essay study - Evidence III - Moderate degree
2013	- Sanz-Marco E, Udaondo P, García-Delpech S, Vazquez A, Diaz-Llopis M. [20] - Pubmed	- Spain - English	- Cohort study - Evidence IV - Moderate degree
2012	- Sabti S, Halter JP, Fränkl BCB, Goldblum D. [21] - Scopus/Web of Science	- Switzerland - English	- Cohort study - Evidence IV - Moderate degree
2012	- Na KS, Kim MS. [22] - Scopus/Web of Science/PUBMED/CINAHL	- South Korea - English	- Case-control study - Evidence IV - Moderate degree
2010	- Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A. et al. [23] - Scopus/Web of Science	- USA - English	- Case-control study - Evidence IV - Moderate degree
2009	- Dastjerdi MH, Hamrah M, Dana R. [24] - Pubmed	- USA - English	- Cohort study - Evidence IV - Moderate degree
2007	- Takahide K, Parker PM, Wu M, Hwang WYK, Carpenter PA, Moravec C. et al. [25] - Scopus	- USA - English	- Cohort study - Evidence IV - Moderate degree
2006	- Leite SC, Castro RS, Alves M, Cunha DA, Correa MEP, Silveira LA, et al. [26] - Scopus/Web of Science	- Brazil - English	- Case-control study - Evidence IV - Moderate degree
2006	- Lelli Júnior GJ, Musch DC, Gupta A, Farjo QA, Nairus TM, Mian SI. [27] - Scopus	- USA - English	- Cohort study - Evidence IV - Moderate degree
2006	- Rao SN, Rao RD. [28] - Scopus	- USA - English	- Cohort study - Evidence IV - Moderate degree
2015	- Yamane M, Ogawa Y, Fukui M, Kamoi M, Saijo-Ban Y, Yaguchi S. et al. [5] - Pubmed	- Japan - English	- Case study - Evidence VI - Weak degree
2014	- Grob S, Dana R. [29] - Cinahl	- USA - English	- Case study - Evidence VI - Weak degree
2012	- Yaguchi S, Ogawa Y, Kamoi1 M, Uchino M, Tatematsu Y, Ban Y. et al. [30] - Scopus	- Japan - English	- Case series study - Evidence VI - Weak degree
2007	- Jacobs DS, Rosenthal P. [31] - Scopus/Web of Science	- USA - English	- Case series study - Evidence VI - Weak degree
2007	- Chiang CC, Lin JM, Chen WL, Tsai YY. [32] - Scopus	- China - English	- Case study - Evidence VI - Weak degree
2001	- Ogawa Y, Okamoto S, Kuwana M, Mori T, Watanabe R, Nakajima T. et al. [33] - Scopus/Web of Science	- Japan - English	- Case study - Evidence VI - Weak degree

Results

Out of 1.551 articles identified, there were 57 included in the first selection (title and abstract reading). Of them, 33 were excluded because they were repeated in the bases. Thus, 24 were elected to reading the full text, however, three were excluded because they did not fit the inclusion criteria and answer the guiding question adopted. Thus, the final review sample was composed of 21 studies of selected for reading in its full.

Table 1 shows the consolidated of the studies included in the review. Regarding the country of such studies, it was found that seven (33.33%) were developed in Japan, followed by six (28.57%) in the United States of America (USA), two (9.52%) in China, two (9.52%) in South Korea, one (4.76%) in Brazil, one (4.76%) in Italy, one (4.76%) in Switzerland and one (4.76 %) in Spain. According to the language and year of publication, it was found that all articles (100%) were in English, and ten (47.61%) were published in the last five years.

As for the method used, six articles (28.57%) used the clinical essay, six (28.57%) were cohort studies, four (19.04%) were case studies, three were case-control (14.28%) and two were series of cases (9.52%). Concerning to the evidence level/degree of recommendation, fifteen articles (71.42%) showed evidence level III and IV and a moderate degree of recommendation and the rest had evidence level VI and low degree of recommendation. **(Table 1)**

Figure 2 represents the consolidation of the types of treatments used in the studies. It was shown more frequently to the use of Cyclosporin 0.05% in all four studies (19.04%), followed by allogeneic drops in two studies (9.52%) and two other autologous drops (9.52%). Other therapeutic appeared only in one study each (4.76%).

Discussions

The identification and analysis of the studies´ components in this review identified the scientific evidence for the treatment of dry eye in patients after HSCT. Several dry eye treatment strategies were found, such as the use of topical cyclosporine, linoleic acid, omega-3 fatty acids, androgens, some types of tetracyclines and steroids [34]. However, a consensus to define the best treatment for dry eye in the reviewed studies has not identified. The choice of appropriate treatment will depend in particular clinical characteristics presented in the post-transplantation with chronic ocular graft-versus-host.

The use of cyclosporine 0.05% occurred more frequently among the studies (19.04%). On this treatment, other studies report that the drug acts as an immunomodulatory agent that blocks the proliferation of T cells and receptor signal transduction [35-36-37-38]. When T cells are activated on the ocular surface in dry eye syndrome, corneal sensitivity is decreased, which results in an exacerbation of dry eye caused by the decrease in reflex tearing, which can cause damage to the ocular surface [35-39- 40]. Thus, cyclosporine results in a reduction of inflammation and an increased tear production [41].

Other studies have demonstrated the efficacy of topical cyclosporine 0.05% in treating dry eye [35-42-43] and corroborated the findings of this review. On the other hand, a survey reveals that in Japan, the use of cyclosporin A is not an approved treatment for dry eye. [44]

Other therapeutic options used are the allogeneic and autologous drops. A cohort study of patients with severe ocular disorder demonstrated the safety of the use of allogeneic serum eye drops for dry eye treatment since there are no universal consensus criteria for selecting patients suitable for autologous blood donation. It is known that therapeutic option is contraindicated in elderly patients, children, and patients with certain disorders. It is noteworthy that the serum from a patient may contain potentially

harmful drug metabolites, as well as the presence of pro-inflammatory mediators [45].

The use of diquafosol ophthalmic solution 3% and rebamipide was reported in a study conducted in Japan as new pharmacological agents for the treatment of dry eye [44]. The solution diquafosol 3% ophthalmic stimulated tear and mucin secretion on the ocular surface directly and rebamipide favored mucin secretion by goblet cells attached directly to the conjunctiva of the eye surface. The eye drops treat selectively the layer of the tear film and increases their stability, making them effective for the treatment of dry eye [46].

The drops tacrolimus 0.03% were also shown as a form of treatment for dry eye. Research reported that tacrolimus, also known as FK506, is an immunosuppressive drug that inhibits the immune response mediated by T cells, about 10 to 100 times more potent than cyclosporine [47].

A retrospective study also described the effectiveness and safety of topical tacrolimus ointment 0.02% in patients with GVHD with chronic eye inflammation of the ocular surface but reported that the concentration of tacrolimus for the control of ocular diseases caused by immune system even has been established [47]. When investigated the efficacy of topical ophthalmic drops of 0.03% tacrolimus to the treatment of dry eye in GVHD in resistant or intolerant patients to topical cyclosporine 0.05%, there is evidence that these resistant or intolerant patients to Cyclosporin can be effectively treated by the use of tacrolimus 0.03% [20].

Regarding the use of rich autologous plasma drops in growth factors, its effect is similar to the use of allogeneic eye drops, as mentioned above. However, the growth factors present also contribute to the renewal of the corneal epithelial cells because they are involved in the proliferation, differentiation, migration, and apoptosis [16-48].

Another therapeutic measure identified was occlusion of lachrymal puncta. As shown by the study, caps are placed on the upper or lower points to occlude the opening to decrease the output of the few tears produced, increasing the retention time, and thus moisture outside the eye [49].

Mesenchymal stromal cells act as sulfasalazine, making them remedial once limited to tissue destruction and enhance the repair in various diseases [50]. Thus, these cells protect the ocular surface inflammation by suppressing the dry eye disease [51].

The use of Tranilast® inhibits the production and release of inflammatory mediators, eye cytokines and inhibits collagen synthesis. Although not widely studied, a study has shown that its use improved tearing reflection. Moreover, the topic Tranilast® can act in preventing fibrosis of the surface around the holes of the tear ducts near the exterior ocular surface, where the intact acini of the lacrimal gland are present in the light phase of dry eye. Therefore, this therapy is effective in the initial stage of the dry eye [6].

Treatment with a gas-permeable scleral lens allows control of evaporation, acting as a permeable protective covering gas to the cornea and conjunctiva. The protection against evaporation and mechanical trauma to the eyelid blinking allows the regeneration of corneal defects in the presence of appropriate gas infusion [25]. Another study that evaluated the use of this lens for the severe dry eye by aqueous deficiency reported benefits for rehabilitation of dry eye [52].

The umbilical cord serum eye drops also recommended as a treatment for dry eye is targeted with many advantages over the peripheral blood serum. It contains higher concentrations of neurotrophic growth factors and promotes proliferation and differentiation of corneal epithelium [53-54].

Another form of treatment used was the association between FK506 and corticosteroids, which has proven effective in the treatment of severe dry eye in patients with chronic GVHD. The beneficial effect of corticosteroids reported on the findings [33] corroborates those described in other studies,

the use of which is recommended especially when there is a proliferation of signs of inflammation [55].

Another review article reported that corticosteroids continue to be essential for the control of chronic GVHD. Systemic use is the base of treatment of acute exacerbations of chronic GVHD. However, there is insufficient data to demonstrate the efficacy of topical steroids in chronic GVHD eye [56].

Conclusion

In this review, various types of treatments used for dry eye in patients after HSCT became clear. However, there is no consensus as to the best type of treatment for these patients. It is known that the appropriate therapy will depend primarily on the clinical characteristics presented when in a post-operative situation with chronic graft-versus-host eye.

Evidence identified demonstrated a degree of recommendation from moderate to weak, which suggests the urgent need for studies with designs that have a high level of evidence and the degree of strong recommendation to be stronger evidence established for the treatment of dry eye in the types of patients covered in this review, considering the high frequency of this syndrome.

References

1. Voltarelli JC, Pasquini R, Ortega ETT. Transplante de células-tronco hematopoéticas. São Paulo: Atheneu; 2009. 1280p.
2. Santos CLT, Sawada NO, Santos JLF. Evaluation of the health-related quality of life of hematopoietic stem cell transplantation patients. Rev Latino-Am Enfermagem. 2011; 19(6): 1322-8.
3. Ministério da Saúde (BR). Portaria Nº 931 de 2 de maio de 2006. Aprova o Regulamento Técnico para Transplante de Células-Tronco Hematopoéticas. Brasília: Ministério da Saúde; 2006. 16p.
4. Azevedo W. Doença enxerto versus hospedeiro aguda A-GVHD. Rev Bras Hematol Hemoter. 2010; 32(Supl. 1): 16-21.
5. Yamane M, Ogawa Y, Fukui M, Kamoi M, Saijo-Ban Y, Yaguchi S. et al. Long-term rebamipide and diquafosol in two cases of immune-mediated dry eye. Optom Vis Sci. 2015; 92(4): 25-32.
6. Ogawa Y, Dogru M, Uchino M, Tatematsu Y, Kamoi m, Yamamoto Y. et al. Topical tranilast for treatment of the early stage of mild dry eye associated with chronic GVHD. Bone Marrow Transplant. 2010; 45: 565-9.
7. Fonseca EC, Arruda GV, Rocha EM. Olho seco: etiopatogenia e tratamento. Arq Bras Oftalmol. 2010; 73(2): 197-203.
8. França CFSM, Fernandes APNL, Carvalho DPSRP, Xavier SSM, Ferreira Junior MA, Botarelli FR, et al. Evidence of interventions for the risk of dry eye in critically ill patients: an integrative review. Applied Nursing Research. 2016; 29: 14-7.
9. Broome ME. Integrative literature reviews for the development of concepts. In Rodgers BL, Knafl KA. Editors. Concept Development in Nursing. W.B. Saunders Co., Philadelphia, PA.1993; pp. 231-50.
10. Whittemore R, Knafl K. The integrative review: updated methodology Methodological issues in nursing research. J Adv Nurs. 2005; 52(5): 546-53.
11. Kitchenham, B. Procedures for performing systematic review. Software Engineering Group, Department of Computer Science, Keele University, Keele (UK); 2004.
12. Ham W, Jordan P. Systematic review as a research method in postgraduate nursing education. Health SA Gesondheid. 2015; (20).
13. Ministério da Saúde (BR). Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Ciência e Tecnologia. Diretrizes metodológicas: elaboração de revisão sistemática e metanálise de ensaios clínicos randomizados. Brasília: Ministério da Saúde; 2012.
14. Melnyk BM, Fineout-Overholt E, Stillwell SB, Williamson KM. Evidence-based practice: step by step. Am J Nurs. 2010; 110(5): 51-3.
15. Ogawa Y, Okamoto S, Mori T, Yamada M, Mashima Y, Watanabe R. et al. Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. Bone Marrow Transplant. 2003; 31: 579-83.
16. Pezzotta S, Fante CD, Scudeller L, Cervio M, Antoniazzi ER, Perotti C. Autologous platelet lysate for treatment of refractory ocular GVHD. Bone Marrow Transplant. 2012; 47: 1558-63.
17. Weng J, He C, Lai P, Luo C, Guo R, Wu S. et al. Mesenchymal stromal cells treatment attenuates dry eye in patients with chronic graft-versus-host disease. Mol Ther. 2012; 20(12): 2347-54.
18. 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: 293-302.

19. Yoon KC, Jeong IY, Im SK, Park YG, Kim HJ, Choi J. Therapeutic effect of umbilical cord serum eyedrops for the treatment of dry eye associated with graft-versus-host disease. Bone Marrow Transplant. 2007; 39: 231-5.
20. Sanz-Marco E, Udaondo P, García-Delpech S, Vazquez A, Diaz-Llopis M. Treatment of Refractory Dry Eye Associated with Graft Versus Host Disease with 0.03% Tacrolimus Eyedrops. J Ocul Pharmacol Ther. 2013; 29(8): 776-83.
21. Sabti S, Halter JP, Fränkl BCB, Goldblum D. Punctal occlusion is safe and efficient for the treatment of keratoconjunctivitis sicca in patients with ocular GvHD. Bone Marrow Transplant. 2012; 47: 981-4.
22. Na KS, Kim MS. Allogeneic serum eye drops for the treatment of dry eye patients with chronic graft-versus-host disease. J Ocul Pharmacol Ther. 2012; 28(5): 479-83.
23. Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A. et al. Treatment of ocular graft-versus-host disease with topical cyclosporine 0.05%. Cornea. 2010; 29(12): 1392-6.
24. Dastjerdi MH, Hamrah M, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. Cornea. 2009; 28(10): 1091-6.
25. Takahide K, Parker PM, Wu M, Hwang WYK, 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: 1016-21.
26. Leite SC, Castro RS, Alves M, Cunha DA, Correa MEP, Silveira LA, et al. Risk factors and characteristics of ocular complications, and efficacy of autologous serum tears after haematopoietic progenitor cell transplantation. Bone Marrow Transplant. 2006: 38: 223-7.
27. Lelli Júnior GJ, Musch DC, Gupta A, Farjo QA, Nairus TM, Mian SI. Ophthalmic cyclosporine use in ocular GVHD. Cornea. 2006; 25(6): 635-8.
28. 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(6): 74-8.
29. Grob S, Dana R. A pharmacological approach to dry eye syndrome in GVHD. Ophthalmology Times. 2014; 15: 6-8.
30. Yaguchi S, Ogawa Y, Kamoi1 M, Uchino M, Tatematsu Y, Ban Y. et al. Surgical management of lacrimal punctal cauterization in chronic GVHD-related dry eye with recurrent punctal plug extrusion. Bone Marrow Transplant. 2012; 47(11): 1465-9.
31. Jacobs DS, Rosenthal P. Boston scleral lens prosthetic device for treatment of severe dry eye in chronic graft-versus-host disease. Cornea. 2007; 26(10): 1195-9.
32. 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.
33. Ogawa Y, Okamoto S, Kuwana M, Mori T, Watanabe R, Nakajima T. et al. Successful treatment of dry eye in two patients with chronic graft-versus-host disease with systemic administration of FK506 and corticosteroids. Cornea. 2001; 20(4): 430-4.
34. Alves JS. Olho seco: uma abordagem didática. Rio de Janeiro: E-papers; 2010.
35. Wan KH, Chen LJ , Young AL. Efficacy and Safety of Topical 0.05% Cyclosporine Eye Drops in the Treatment of Dry Eye Syndrome: A Systematic Review and Meta-analysis. Ocul Surf. 2015; 13(3): 213-25.
36. Stepkowski SM. Molecular targets for existing and novel immunosuppressive drugs. Expert Rev. Mol. Med. 2000; 2: 1-23.
37. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. Immunopharmacology. 2000; 47: 119-25.
38. Nussenblatt RB, Palestine AG. Cyclosporin: immunology, pharmacology and therapeutic uses. Surv Ophthalmol. 1986; 31(3): 159-69.
39. Song XJ, Li DQ, Farley W, Luo LH, Heuckeroth RO, Milbrandt J. Neurturin-deficient mice develop dry eye and keratoconjunctivitis sicca. Invest Ophthalmol Vis Sci. 2003; 44: 4223-9.
40. Prabhasawat P, Tseng SC. Frequent association of delayed tear clearance in ocular irritation. Br J Ophthalmol. 1998; 82: 666-75.
41. Rodriguez-Aller M, Kaufmann B, Guillarme D, Stella C, Furrer P, Rudaz S, et al. In vivo characterisation of a novel water-soluble Cyclosporine A prodrug for the treatment of dry eye disease. European Journal of Pharmaceutics and Biopharmaceutics. 2012; 80: 544-52.
42. Deveci H, Kobak S. The efficacy of topical 0.05 % cyclosporine A in patients with dry eye disease associated with Sjögren's syndrome. Int Ophthalmol. 2014; 34:1043-8.
43. Perez-Rico C, Germain F, Castro-Rebollo M, Moreno-Salgueiro A, Teus MA. Effect of topical 0.05% cyclosporine A on corneal endothelium in patients with dry eye disease. Int J Ophthalmol. 2013; 6(4): 471-4.
44. Dogru M, Nakamura M, Shimazaki J, Tsubota K. Changing trends in the treatment of dry-eye disease. Expert Opin Investig Drugs. 2013; 22(12): 1581-601.
45. Harritshøj LH, Nielsen C, Ullum H, Hansen MB, Julian HO. Ready-made allogeneic ABO-specific serum eye drops: production from regular male blood donors, clinical routine, safety and efficacy. Acta Ophthalmol. 2014; 92: 783-6.
46. Koh S. Clinical utility of 3% diquafosol ophthalmic solution in the treatment of dry eyes. Clinical Ophthalmology. 2015; 9: 865-72.
47. Jung JW, Lee YJ, Yoon SC, Kim T, Kim EK, Seo KY. Long-term Result of Maintenance Treatment With Tacrolimus Ointment in Chronic Ocular Graft-Versus-Host Disease. American Journal of Ophthalmology. 2015; 159(3): 519-27.

48. Yu FS, Yin J, Xu K, Huang J. Growth factors and corneal epithelial wound healing. Brain Res Bull 2010; 81: 229-35.
49. Behrens A, Doyle JJ, Stern L, Chuck RS, McDonnell PJ, Azar DT et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 2006; 25: 900-7.
50. Prockop, DJ, Kota, DJ, Bazhanov, N and Reger, RL (2010). Evolving paradigms for repair of tissues by adult stem/progenitor cells (MSCs). J Cell Mol Med. 14 : 2190-99.
51. Lee MJ, Ko AY, Ko JH, Lee HJ, Kim MK, Wee WR et al. Mesenchymal Stem/Stromal Cells Protect the Ocular Surface by Suppressing Inflammation in an Experimental Dry Eye. Molecular Therapy. 2015; 23(1): 139-46.
52. Hänisch KT, Neppert B, Geerling G. Gasdurchlässige Sklerallinsen als konservative Therapiealternative bei extremen Hornhautektasien und schwerem Tränenmangel. Ophthalmologe 2005; 102: 387-92.
53. Shen EP, Hu FR, Lo SC, Chen YM, Sun YC, Lin CT, Chen WL. Comparison of corneal epitheliotrophic capacity among different human blood-derived preparations. Cornea. 2011; 30: 208-14.
54. Yoon K, Oh J, PARK J, Choi J. Application of umbilical cord serum eyedrops after laser epithelial keratomileusis. 2013; 91: 22-8.
55. Steven P, Sauerbier L, Siebelmann S, Gehlsen U, Tahmaz V, Wittig S. Therapie der okulären Graft-versus-Host-Erkrankung. Klin Monatsbl Augenheilkd. 2015; 232: 658-63.
56. Espana EM, Shah S, Santhiago MR, Singh AD. Graft versus host disease: clinical evaluation, diagnosis and management. Graefes Arch Clin Exp Ophthalmol. 2013; 251: 1257-66.