

Hemoderivatives Eye Drops for the Treatment of Severe Dry Eye Disease in Patients with Chronic Graft Versus Host Disease

Silvana Guerriero* and Rosa Anna Favale

Department of Basic Medical Sciences, Neuroscience and Sensory Organs, U.O. Ophthalmology, University of Bari, Italy

***Corresponding Author:** Silvana Guerriero, Department of Basic Medical Sciences, Neuroscience and Sensory Organs, U.O. Ophthalmology, University of Bari, Italy.

Received: January 18, 2018; **Published:** March 09, 2018

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative approach for several hematologic neoplasms. Despite technology has progressed considerably during the last decades, graft versus-host disease (GVHD) remains the most important cause of morbidity and mortality after transplantation [1].

Although acute GVHD (aGVHD) has a considerable impact on non-relapse mortality, chronic GVHD (cGVHD) is the most common long-term complication and occurs in 30% to 70% of adults who survive for more than 100 days after receiving their transplantation [2].

Ocular manifestations of acute GVHD are uncommon and might be associated with irreversible ocular damage while they are among the most common complications of chronic GVHD, reported in up to 60% to 80% of patients [3].

Patients with ocular chronic GVHD suffer from visual deterioration, lacrimal gland dysfunction, meibomian gland dysfunction, corneal epitheliopathy, conjunctival scarring, and hyperemia. These conditions have a large detrimental impact on patients' quality of life.

This severe form of dry eye disease results from the infiltration of the lacrimal gland by fibroblasts and T lymphocytes; these infiltrates cause impaired secretory function and corneal damage [4].

Current ocular GVHD treatments are suboptimal and still not standardized, mainly based on the control of lubrication and inflammation, although the expected results are not optimal and often ineffective. Application of artificial tears provide additional lubrication. Steroids are the most commonly anti-inflammatory eye drops prescribed for short-term treatment, but their long-term use is not recommended. Cyclosporine A .05% [5] and tacrolimus .03% eye drops [6] are immunosuppressive drug used as an anti-inflammatory topical drop. However, adverse ocular events have been reported.

This has led to the use of other therapeutic strategies based on hemoderivatives [7].

The use of drops of different blood derivatives has resulted in a remarkable advance in the management of severe cases because blood-derived therapies contain some of the same growth factors, cytokines, vitamins and nutrients found in natural tears to support epithelial cell homeostasis, growth and migration [8].

Currently, the most common preparations are the use of autologous or allogeneic serum drops, and platelet-derived plasma products.

Autologous serum eye drops, First described by Fox., *et al.* [9] and later by Tsubota., *et al.* [10] has biochemical properties similar to those of human tears, importantly, TGF- β concentrations in autologous serum are five times higher in serum than in tears. Therefore, many ophthalmologists prefer to use a 20% dilution [11].

Autologous serum has been shown to be effective in controlling symptoms, but not on the corneal damage in place, it also requires a high frequency of instillations [12].

Allogeneic preparations of serum eye drops are indicated when autologous preparation is inconvenient for the patient because of coexisting medical conditions.

Platelet-Rich Plasma include a variety of products and denominations derived from the patient's own blood, which can be obtained by centrifugation to obtain a plasma fraction with a platelet concentration higher than that in the circulating blood [13].

These preparations have been used successfully because of the high levels of growth factors found in platelets.

Platelets can be artificially activated and release their contents housed in alpha granules, rich in a large pool of proteins and factors including EGF, PDGF, TGF secrete, vascular endothelial growth factor (VEGF), IGF-1, hepatic growth factor (HGF), nerve growth factor (NGF), and platelet factor 4 (PF-4) involved in the wound healing process of the cornea and conjunctival surface.

One of the most interesting preparation is an autologous platelet concentrate, lysed, and then reconstituted as eyes drops (PClys) [14].

For the preparation of PClys eye drops, patients are subjected to a blood sample in a whole blood tubes, to which it is previously added anticoagulant. The test tubes come subsequently centrifuged and each one extracts the plasma rich in platelets which is concentrated in a single 50 ml container. Then a freeze-thaw (-80°C/+37°C) passage is performed, which determines the breakage of the platelets and allows the growth factors to escape, (platelet lysate). At the end of the thawing, it is diluted (at 30% - 40%), by adding 0.9% sodium chloride. The diluted platelet lysate is divided into cryovials obtaining 1 ml sterile disposable aliquots, which must be stored in the freezer at -20 C for up to 3 months maintaining constant or slight variations in the concentration of the most important growth factors.

Patient are provided for storage: the sterile vials can be frozen in home freezers at -4°C for up to 30 days and topical application (2 eye drops per eye, 3 times each day)

Different investigations have evaluated the safety and efficacy of the use of PClys eye drops, with a rapid and persistent improvement of subjective symptoms as visual acuity, photophobia, pain, foreign body sensation, and dry eyes (xerophthalmia), (resulting in a considerable improvement in quality of life) and objective symptoms as increase of BUT, fluorescein staining. The Schirmer's test value did not improve in those patients because of the fibrosis of the lacrimal glands.

Based on the excellent toxicity profile and rapid response achieved with of PClys eye drops can be considered a well tolerated therapeutic option in patient with cGVHD.

Combination therapy with tacrolimus or CyA ointment, currently being used as a maintenance-treatment for ocular cGVHD, could also be considered [15].

Bibliography

1. Arnaout K, *et al.* "Complications of allogeneic hematopoietic stem cell transplantation". *Cancer Investigation* 32.7 (2014): 349-362.
2. Anderson NG and Regillo C. "Ocular manifestations of graft versus host disease". *Current Opinion in Ophthalmology* 15.6 (2004): 503-507.
3. Ogawa Y, *et al.* "Dry eye after haematopoietic stem cell transplantation". *British Journal of Ophthalmology* 83.10 (1999): 1125-1130.

4. Ogawa Y, *et al.* "Periductal area as the primary site for T-cell activation in lacrimal gland chronic graft-versus-host disease". *Investigative Ophthalmology and Visual Science* 44.5 (2003): 1888-1896.
5. Malta JB, *et al.* "Treatment of ocular GVHD with topical cyclosporine 0.05%". *Cornea* 29.12 (2010): 1392-1396.
6. Zhou XQ and Wei RL. "Topical cyclosporine A in the treatment of dry eye: A systematic review and meta-analysis". *Cornea* 33.7 (2014): 760-767.
7. Sanz-Marco E, *et al.* "Treatment of refractory dry eye associated with GVHD with 0.03% tacrolimus eye drops". *Journal of Ocular Pharmacology and Therapeutics* 29.8 (2013): 776-783.
8. Pflugfelder SC. "Antiinflammatory therapy for dryeye". *American Journal of Ophthalmology* 137.2 (2004): 337-342.
9. Fox RI, *et al.* "Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca". *Arthritis and Rheumatology* 27.4 (1984): 459-461.
10. Tsubota K, *et al.* "Treatment of dry eye by autologous serum application in Sjogren's syndrome". *British Journal of Ophthalmology* 83.4 (1999): 390-395.
11. Anitua E, *et al.* "Biological stability of plasma rich in growth factors eye drops after storage of 3 months". *Cornea* 32.10 (2013): 1380-1386.
12. F Zallio, *et al.* "A Single-Center Pilot Prospective Study of Topical Application of Platelet-Derived Eye Drops for Patients with Ocular Chronic Graft-versus-Host Disease". *Biology of Blood and Marrow Transplantation* 22.9 (2016): 1664-1670.
13. Alio JL, *et al.* "Eye platelet-rich plasma in the treatment of ocular surface disorders". *Current Opinion in Ophthalmology* 26.4 (2015): 325-332.
14. A Sangiovanni, *et al.* "GvHD cronica: il lisato piastrinico nella terapia della superficie oculare". *Bollettino della Società Medico Chirurgica di Pavia* 125.3 (2012): 541-549.
15. Jung JW, *et al.* "Long-term result of maintenance treatment with tacrolimus ointment in chronic ocular graft-versus-host disease". *American Journal of Ophthalmology* 159.3 (2015): 519-527.

Volume 9 Issue 4 April 2018

©All rights reserved by Silvana Guerriero and Rosa Anna Favale.