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REVIEW

Umbilical Cord Blood and Serum for the Treatment of Ocular Diseases: A Comprehensive Review

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ABSTRACT

Several blood derivatives have been proposed for the treatment of various ocular diseases that affect either the anterior or the posterior segment of the eye. Blood sources may range from the patient's own peripheral blood (autologous) to donor tissues, mainly allogeneic peripheral blood and umbilical cord blood (UCB). The utilization of the latter permits the collection of a large amount of serum all at once, and is characterized by therapeutic feasibility in patients with a poor general condition or anemia and blood dyscrasia. Products derived from UCB have two potential uses. First, serum in the form of eye drops can be applied topically onto the ocular surface to efficiently treat anterior segment disorders such as dry eye syndrome or corneal epithelial defects with different etiologies. The rationale for and efficacy of this application derive from the high concentrations of biologically active components and growth factors in UCB, which can nourish the ocular surface. Second, UCB is a source of stem cells, which are used in the field of regenerative medicine because they differentiate into various mature cells, including corneal and retinal cells. Therefore, UCB-derived stem cells have been proposed as a replacement therapy for the treatment of retinal and optic nerve diseases, given that current standard treatments often fail. The present review explores the clinical results that have been obtained using UCB-derived products in the field of ophthalmology, as well as the current limitations of those products in this field. Furthermore, given the promising development of UCB-based therapies, possible future directions in this area are discussed.

Keywords: Allogeneic serum; Cornea; Ocular surface disease; Optic nerve; Retina; Stem cells; Umbilical cord blood; Umbilical cord blood serum

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Key Summary Points

The use of umbilical cord blood (UCB) derivatives for the treatment of ocular diseases has become increasingly popular in recent years.

These derivatives include serum-based eye drops for the treatment of ocular surface disorders and stem-cell-based products for regenerating injured corneal, retinal, and optic nerve tissues.

Studies evaluating the use of UCB-derived stem cells in human models are required.

There is a need for a standardized therapeutic protocol that specifies the optimal formulation, dilution, and treatment duration for serum eye drops derived from UCB.

INTRODUCTION

Whole blood and various derivatives of it are used to treat a wide range of ophthalmic diseases that affect the ocular surface, the retina, and the optic nerve. Blood for ophthalmic clinical use can be extracted from the patient's own peripheral blood (autologous blood) or from donors (allogeneic peripheral blood or umbilical cord blood, UCB). The most widely used blood-derivative products are fibrin-based products, albumin, serum, cryoprecipitate, platelets, plasmin, and fresh frozen plasma. Among platelet products, platelet-rich plasma (PRP) has a high concentration of essential growth factors and cell adhesion molecules, which is achieved by concentrating platelets into a small volume of plasma. PRP is applied as eye drops or clots to aid wound healing by enhancing the physiological process at the site of an injury [1].

The ocular application of blood and its derivatives ranges from instillation to the ocular surface in the form of eye drops (e.g., serum) to the use of whole blood on the retina during vitreoretinal surgery. The idea of using products derived from blood to treat ocular disease was first described over 40 years ago by Ralph and coauthors, who developed a mobile ocular perfusion pump to deliver autologous serum (AS) to the ocular surfaces of patients affected by chemical burns [2]. Since then, the application of eye drops derived from AS (UCB serum, UCBS) or allogeneic serum (allo-S) to treat a wide range of ocular surface diseases, mainly severe dry eye due to either Sjögren syndrome (SS) or ocular graft-versus-host disease (oGVHD), has been explored [3–7]. More recently, stem cells obtained from different sources, including UCB, have been used in cell replacement therapies for a variety of ocular pathologies (ranging from corneal scar to optic nerve degeneration) that are traditionally characterized by poor outcomes when treated with conventional therapies [8–17]. In the present review, we summarize the various types of products obtained from UCB and their current indications for the treatment of ocular diseases.

LITERATURE REVIEW: METHODS

In this review article, a systematic computerized search of the literature was conducted from inception until November 2019. All English-language articles dealing with the topic of UCB derivatives in the treatment of ocular diseases were retrieved from the electronic databases PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trilals and then checked for applicability by the authors. The searches were performed by two independent investigators (G.G. and C.S.). The following keywords and MeSH terms were used: 'allogeneic serum,' 'cornea,' 'ocular surface disease,' 'optic nerve,' 'retina,' 'stem cells,' 'umbilical cord blood,' and 'umbilical cord blood serum.' All pertinent articles were thoroughly assessed, and their reference lists were scritinized to identify any other studies that were applicable to this review. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

UCB

The main application of UCB is hematopoietic stem cell (HSC) transplantation for the treatment of a variety of malignant and benign hematological disorders. The Center for International Blood and Marrow Transplant Research reported that over 8000 allogeneic transplant procedures were performed in the US in 2016 [18]. However, it is noteworthy that besides being a rich source of HSCs and hematopoietic progenitor cells, UCB is also a source of other cells with broad-ranging proliferation and differentiation capacities. These include mesenchymal stromal cells, capable of producing cells of the osteogenic, adipogenic, and chondrogenic lineages, and unrestricted somatic stem cells, a primitive cell type that expresses some features of pluripotent embryonic stem cells. Stem cells are undifferentiated cells that are defined by their ability to self-renew and differentiate into mature cells. They are attractive because of their high proliferative capacity, implying that an inexhaustible number of mature cells can be generated from a given stem cell source. Thus, cell replacement therapy has been proposed in recent years as a viable alternative treatment for various retinal pathologies, especially Stargardt's disease, retinitis pigmentosa, and age-related macular degeneration (AMD). An effective treatment of AMD is of particular importance since it is a leading cause of irreversible vision loss among the elderly. Although the pathogenesis of AMD is yet to be fully elucidated, there is increasing evidence of the involvement of retinal pigment epithelium (RPE) cells, which are known to play a key role in promoting and supporting photoreceptor cell survival. As a result, dysfunction and loss of RPE cells can lead to photoreceptor degeneration and subsequent decreased vision. Stem cell therapy that represents a combined rescue and cell replacement strategy has been proposed as a means to manage vision-threatening complications of AMD. Additionally, RPE cells derived from stem cells are able to produce neurotrophic factors that support photoreceptor survival through the paracrine effect. Koh et al. investigated whether treatment with cells derived from human umbilical tissue was able to preserve photoreceptors and synaptic connectivity in a rat model of retinal degeneration caused by *Mertk* loss of function. Subretinal transplantation of cells derived from umbilical tissue was shown to rescue visual function by preserving retinal synaptic connectivity and attenuating glial reactivity. Multiple injections provided enhanced effects, thus confirming the potential therapeutic application of these cells in the setting of human retinal degeneration [19]. Recently, ischemic retinopathies such as diabetic retinopathy, retinopathy of prematurity, and retinal vein occlusion have been treated using vasoregenerative cell therapy [20–24]. Furthermore, cell therapy has emerged as a promising tool for optic nerve regeneration and is expected to fill current gaps in the field of optic nerve protection. Zhang and coauthors evaluated the effects of intravitreal injection of neural stem cells originating from UCB-derived mesenchymal cells on neurodegeneration in diabetic retinopathy in rats. The treated group exhibited attenuated vascular dysfunction 4 weeks following the transplantation procedure and increased levels of brain-derived neurotrophic factor (BDNF) compared to untreated rats. Moreover, morphologic retinal improvements were accompanied by signs of improved vision, as documented by flash electroretinogram. Several studies have since been conducted to evaluate the efficacy of UCB-based therapy in treating optic nerve injury with various etiologies. Chung and coauthors detected increased axon survival rates and decreased ganglion cell apoptosis in a model of optic nerve crush injury following a single intravitreal injection, whereas Zhang and Lv pointed out the positive effect of UCB treatment on optic nerve biomechanical properties, as shown by the increased maximum load, stress, and strain and the greater elasticity [8, 12, 13]. Furthermore, Ji and coauthors investigated the potential therapeutic benefits of intravitreally transplanted UCB-derived mesenchymal stem cells in an animal model of elevated intraocular pressure, which is a well-known risk factor for both the onset and progression of glaucomatous optic nerve damage. The transplantation procedure revealed a neuroprotective effect that

Table 1 Results of animal studies of the application of UCB therapy to ocular diseases

Study (year)	Design	Condition	Population (*n*)	Treatment	Control arm	Route	Frequency	Results
Zhu (2011) [10]	Prospective comparative randomized	Traumatic optic neuropathy	Mice (48)	hUCB-MSCs	Injured-only group, neurotrophic factor-treated group, and group treated with neurotrophic factor plus hUCB-MSCs	Intravitreal	Single injection	Significant improvement in fVEP testing in treated groups compared with nontreated group. hUCB and neurotrophic factor mixture achieved the best results
Zhao (2011) [17]	Prospective comparative randomized	ON injury	Mice (135)	hUCB-MSCs	Sham surgery group and unmanipulated mice receiving physiological saline solution	Intravitreal	Single injection	Increased RGC density, increased BDNF and GDNF mRNA expression, and improvement in pathological retinal changes in the hUCB-MSCs-treated groups
Chen (2013) [16]	Prospective comparative randomized	ON injury	Mice (132)	hUCB-MSCs	Phosphate-buffered saline	Intravitreal	Single injection	Decreased RGC apoptosis and increased RGC survival in the early phase following treatment. Beneficial effect declined over time
Jiang (2013) [15]	Prospective comparative randomized	Traumatic optic neuropathy	Mice (195)	hUCB-MSCs	Sham treatment	Intravitreal	Single injection	Ameliorated fVEP testing; increased RGC count and decreased RGC apoptosis
Zhang (2015) [12]	Prospective comparative randomized	ON injury	Rabbit (48)	hUCB-MSCs	Sham treatment	Intravitreal	Single injection	Decreased ultrastructural ON damage; improved biomechanical properties (increased maximum load, maximum stress, maximum strain, elastic limit load, elastic limit stress, and elastic limit strain) of ON
Shao (2015) [14]	Prospective comparative	Corneal endothelium deficiency	Rabbit (16)	hUCB-EPCs labeled with CD34 immunomagnetic nanoparticles	CD34 immunomagnetic nanoparticle-labeled UCB EPCS without a magnet; EDM stripping without injection of cells; unmanipulated rabbits	Intracameral injection plus magnetic attraction (cells migrate directionally)	Single injection	Treated corneas became relatively transparent, with little edema
Lv (2016) [13]	Prospective comparative randomized	ON injury	Rabbit (60)	hUCB-MSCs	Intravitreal BDNF	1×10^6 hUCB-MSCs intravitreally	Single injection	Recovery of viscoelasticity of ON (increased stress relaxation and creep properties) in treated groups
Chung (2016) [8]	Prospective comparative	ON crush	Mice (90)	hUCB-MSCs	Sham treatment	Intraarterial	Single injection	Increased axon survival rates, increased visual function (GAP-43 upregulation), and increased oxygen availability (HIF-1α upregulation)
Wang (2016) [24]	Prospective comparative randomized	Oxygen-induced retinopathy	Mice (7)	hUCB-MSCs	Unmanipulated mice; phosphate-buffered saline-treated group.	Intravitreal	Single injection	Faster recovery from retinopathy and lower number of neovascular nuclei in UCB-MSCs-treated group

Table 1 continued

Study (year)	Design	Condition	Population (*n*)	Treatment	Control arm	Route	Frequency	Results
Zhang (2017) [9]	Prospective comparative randomized	Diabetic retinopathy	Mice (–)	hUCB-MSCs	Sham treatment	Intravitreal 0.2×10^6 cells in 2 µL	Single injection	Attenuation of retinal vascular dysfunction, BDNF and Thy-1 upregulation; decreased retinal vessel leakage, better visual function based on positive ERG testing
Mohamed (2017) [22]	Prospective comparative	Cryo-induced retinal injury	Mice (48)	hUCB-MSCs	Unmanipulated mice; intravenously treated group	Intravitreal vs intravenous injection	Single injection	Near-normal retinal structure in MSCs-treated group. Modulation of oxidant-apoptotic status: increased expression of Bcl-2, HMOX1, TXN2; downregulation of 3-NT and caspase-3. Increased bFGF
Dong (2017) [23]	Prospective comparative randomized	Diabetic retinopathy	Mice (60)	hUCB-MSCs	2 µL phosphate-buffered saline	Intravitreal 2 µL	Single injection	Ameliorated retinal layer structure; reduced retinal vessel leakage
Reid (2017) [20]	Prospective interventional comparative	Oxygen-induced retinopathy	Mice (–)	hUCB-MSCs	Unmanipulated mice	Intravitreal vs intraarterial	Single injection	Comparable beneficial effects of intravitreal and intravascular administration routes on vascular repair. Fewer human cells observed in the retinal vasculature following systemic delivery
He (2018) [21]	Prospective comparative	Retinal laser injury	Mice (–)	hUCB-MSCs	Sham treatment	Intravitreal 5 µL PBS alone, MSCs-Exos at a concentration of 50 µg/mL, and different concentrations of exosomes (Exo-L: 25 µg/mL, Exo-M: 50 µg/mL, and Exo-H: 75 µg/mL) for 8, 16, and 24 h	Single injection	Downregulated expression of VEGF mRNA in RPE cells induced by MSC-derived exosomes in vivo and ex vivo after blue light stimulation; subsequent CNV reduction and ameliorated visual function
Jì (2018) [25]	Prospective comparative randomized	Ocular hypertension	Mice (54)	hUCB-MSCs	Unmanipulated mice; phosphate-buffered saline-treated group	Intravitreal	Single injection	Increased numbers of RGCs and axons and increased expression of GDNF and BDNF in hUCB-MSCs-treated groups
Koh (2018) [19]	Prospective interventional comparative	Retinal degeneration	Mice (–)	hUCB-MSCs plus steroids and cyclosporine A	Unmanipulated mice	Subretinal	Single or double injection	Preserved retinal synaptic connectivity and decreased Müller glial cell reactivity

Table 1 continued

Study (year)	Design	Condition	Population (*n*)	Treatment	Control arm	Route	Frequency	Results
Huang (2019) [11]	Prospective comparative	ON crush	Mice (/)	hUCB- 2D-MSCs vs hUCB- 3D-MSCs	ON exposed without crush	Intravitreal injection	Single injection	2D-MSCs had stronger promoting effect than 3D-MSCs on RGC survival and ON axonal regeneration. Improved fVEP and sustained secretion of regeneration-stimulating factors (SCGF-β, HGF, MCP-1, IL-8, and SDF-1α). 2D-MSCs induced the activation of key neuroprotection pathways (JAK/STAT3 and MAPK/ERK)

UCB umbilical cord blood, *ON* optic nerve, *hUCB* human umbilical cord blood, *MSCs* mesenchymal stem cells, *RGCs* retinal ganglion cells, *fVEP* flash visual evoked potential, *SCGF-β* stem cell growth factor-β, *HGF* hepatocyte growth factor, *MCP-1* monocyte chemoattractant protein-1, *SDF-1α* stromal cell-derived factor, *VEGF* vascular endothelial growth factor, *RPE* retinal pigment epithelial, *CNV* corneal neovascularization, *BDNF* brain-derived neurotrophic factor, *ERG* electroretinogram recording, *Bcl-2* B cell lymphoma (Bcl)-2 gene, *HMOX* heme oxygenase, *TXN* thioredoxin, *3-NT* 3-nitrotyrosine, *bFGF* basic fibroblast growth factor, *GAP-43* growth-associated protein-43, *HIF-1α* hypoxia-inducible factor-1α, *hUCB-EPCs* human umbilical cord blood endothelial progenitor cells, *EDDM* endothelium-Descemet membrane layer, *GDNF* glial cell line-derived neurotrophic factor

could be related to the secretion of trophic factors such as BDNF and glial cell-derived neurotrophic factor [19, 24, 25]. Table 1 summarizes the main published studies on UCB use in ophthalmic practice.

UCBS

Serum is the noncellular supernatant that is left when whole blood clots. The rationale for applying serum to the ocular surface is that, compared to conventional lubricant treatments, it more closely resembles natural tears due to several of its biochemical constituents [3]. UCBS has been extensively used in the setting of ocular surface diseases and has produced satisfactory results in terms of efficacy and safety [3, 26–43]. Yoon and coauthors were among the first to test the use of UCBS in the management of several ocular surface disorders, such as dry eye with or without SS, oGVHD, persistent epithelial defects, neurotrophic keratitis, and ocular chemical injury. Serum eye drops were administered topically 6–10 times a day over a period ranging from 2 to 6 months. Treated patients showed a faster epithelial healing rate, greater improvement in symptoms, and increased goblet cell density and corneal sensitivity when compared to healthy subjects. In particular, patients with neurotrophic keratitis experienced a 100% healing rate after approximately 1 month of therapy [26–33]. Furthermore, a significant improvement in corneal epitheliopathy (as indicated by a decreased Oxford staining score) and a higher number of nerves with improved morphology and lower tortuosity were reported by our group, who successfully treated moderate-to-severe forms of dry eye disease with UCBS [6]. Furthermore, the efficacy of serum-based therapy was measured objectively as the decreased expression of inflammatory markers such as cytokines and growth factors via histological examination in mouse models [34, 35]. A recent randomized crossover clinical trial compared the efficacy of UCBS and peripheral adult donor blood serum in the treatment of severe dry eye. Overall, signs improved after either treatment, but the UCBS treatment was found to be

superior in terms of ameliorating subjective symptoms and reducing corneal damage [44].

The potential useful role of serum-based therapy is not limited to ocular surface diseases; it extends to neurodegenerative disorders such as glaucoma. A preliminary study that analyzed the effect of UCBS topically administered to glaucoma patients observed positive results, as shown by improvements in visual field test parameters. This efficacy is thought to be related to the high growth factor content of the serum, which potentially exerts a neuroprotective action on the optic nerve [45]. However, the authors stated that the incidentally observed amelioration in these glaucoma patients requires further investigation.

The main advantages of using serum eye drops obtained from donors such as UCBS are related to the elimination of the proinflammatory cytokines and autoantibodies present in the sera of patients with dry eye caused by systemic diseases (e.g., SS and oGVHD), as those proinflammatory cytokines and autoantibodies could cause damage if applied to the ocular surface [6]. This aspect should theoretically discourage the use of AS in these patients, who represent a significant percentage of severe dry eye cases. However, a recent study showed positive effects of AS on both the subjective symptoms and the objective signs of dry eye caused by systemic autoimmune diseases [46]. In another study, an attempt to predict the quality of AS by categorizing patients with SS into active and inactive groups according to the clinical activity of the disease failed to show any significant difference in therapeutic effect between the two groups [47]. Therefore, additional evidence is needed to clarify whether the use of AS can also be advantageous in patients with concomitant systemic diseases. Other advantages include the ability to use these products in patients with poor venous access, anaemia, and blood dyscrasia, and the potential to create a pool with the desired content of each growth factor. In fact, there is marked interindividual variability in growth factor content, which is thought to be the consequence of a combination of genetic, clinical, and pharmacological factors [48, 49]. Therefore, in order to reduce the variability in the biological constituents of the serum, pooling of serum samples from multiple donors is implemented to obtain final serum products containing required levels of the main constituents. This can be achieved in the laboratory by dosing serum with the desired growth factor, but such a procedure is expensive. Recently, preselection of UCBS with the ideal concentration of epidermal growth factor was realized by collecting UCB samples from young mothers (< 30 years) with a high $CD34^+$ cell content (0.05×10^6/mL) following a long labor (> 6 h) [50]. The same approach could be applied to the other growth factors that play a pivotal role in ocular surface homeostasis (e.g., nerve growth factor).

The main disadvantage of allogeneic serum eye drops is the risk of transmitting infections, so it is essential to produce the serum according to good manufacturing practices. There are controversial theories concerning the need for ABO matching between donor and recipient. On the one hand, it is known that serum contains high levels of ABO substances that might act as antigens and initiate immune-complex-mediated inflammation. On the other hand, the sporadic clinical use of ABO-mismatched eye drops has not been associated with overt immune-complex-mediated hypersensitivity. Table 2 summarizes the main published studies on the use of UCBS in ophthalmic practice.

The frequency and duration of treatment depends upon individual circumstances and are not governed by evidence-based guidelines. The Royal College of Ophthalmologists recently provided two examples of protocols for serum-derived eye drops: (1) withdrawal of treatment after 1 year of therapy in patients with ocular surface disease to define induction of remission, before reinstating indefinite treatment if the symptoms relapse; (2) withdrawal of treatment after the ocular surface has healed in patients with persistent corneal epithelial defects, with treatment restored only if the surface shows signs of recurrence. Recently, a research group summarized the current unanswered questions in this field and termed them the 5 W's and 2 H's: Who is the patient? Why is a blood-based treatment needed? When is it appropriate? Where are products dispensed? What is the product of choice? How is the product

Table 2 Results of clinical studies of UCBS therapy in ocular diseases

Study (year)	Design	Condition	Population (*n*)	Control arm	Frequency (duration)	Concomitant therapy	Results
Vajpayee (2003) [39]	Prospective randomized double-blind	PED	Human (59)	Autologous serum	6/day (21 days)	–	Higher percentage of reepithelization in UCBS group
Yoon (2005) [29]	Prospective interventional	PED	Human (14)	–	6/day (until healing)	–	Faster epitheliopathy healing rate
Yoon (2007) [27]	Prospective interventional	NK	Human (28)	–	6–10/day (until healing)	Tear substitutes, levofloxacin	100% healing within 4.4 weeks on average
Yoon (2007) [28]	Prospective interventional comparative	Dry eye	Human (48)	Autologous serum	6–10/day (2 months)	Tear substitutes	Major improvements in symptoms, keratoepitheliopathy score, and goblet cell density in hUCBS-treated group
Yoon (2007) [30]	Prospective interventional noncomparative	GVHD	Human (12)	–	6–10/day (6 months)	Tear substitutes	Significant improvements in symptoms, corneal sensitivity, TBUT, and keratoepitheliopathy scores
Sharma (2011) [40]	Prospective randomized double-blind	Chemical injury	Human (32)	Autologous serum/tear substitutes	10/day (3 months)	Ofloxacin, prednisolone acetate, homatropine hydrobromide, sodium citrate, ascorbate, tear substitutes	Higher percentage of corneal transparency in UCBS group

Table 2 continued

Study (year)	Design	Condition	Population (*n*)	Control arm	Frequency (duration)	Concomitant therapy	Results
Oh (2012) [35]	Prospective interventional comparative randomized	Chemical injury	Mice (24)	hPBS, tear substitutes	4/day (–)	Levofloxacin	Lower ED parameters, haze scores, stromal inflammation, edema, and IL-1β levels in hUCBS group
Yoon (2013) [32]	Prospective interventional comparative	Post-LASEK PED	Human (60)	Conventional therapy (antibiotics, steroid, and artificial tear eyedrops)	4–6/day (–)	Conventional therapy (antibiotics, steroid, and artificial tear eyedrops)	Longer TBUT and lower keratoepitheliopathy and TGF-β1 levels in hUCBS-treated group
Versura (2013) [42]	Prospective interventional	PED	Human (30)	–	8/day (1 month)	–	Significant reduction in epithelial damage
Erdem (2014) [41]	Prospective interventional	PED	Human (14)	–	5–10/day (21 days)	Tear substitutes, lomefloxacin	75% healing within 12 days
Mukhopadhyay (2015) [7]	Prospective interventional comparative randomized	Dry eye	Human (144)	Autologous serum, tear substitutes	6/day (6 weeks)	–	Significant improvements in clinical parameters and tear protein profile (lysozyme and lactoferrin upregulation, sustained increase in total tear protein level) in serum-treated groups

Table 2 continued

Study (year)	Design	Condition	Population (*n*)	Control arm	Frequency (duration)	Concomitant therapy	Results
Giannaccare (2017) [6]	Prospective interventional open-label	cGVHD, Sjögren syndrome, diabetic keratopathy, neurotrophic keratitis	Human (20)	–	8/day (2 months)	–	Significant decreases in OSDI, VAS, and Oxford grading values. Significant increases in corneal sensitivity, ST, and BUT scores. Higher total number of nerves as well as improved morphology and lower tortuosity. Presence of neuromas and higher dendritic cell density at baseline associated with greater reduction in OSDI after treatment
Kamble (2017) [43]	Prospective interventional comparative randomized	Post-keratoplasty PED	Human (105)	Autologous serum, tear substitutes	6/day (until healing)	–	Decreased ED size and faster reepithelialization in serum-treated groups
Han (2019) [34]	Prospective interventional comparative randomized	Chemical injury	Mice (28)	hAM; hPBS; saline	4/day (7 days)	–	Major decrease in epithelial defect areas in hUCBS group compared with hAM, hPBS, and saline groups. Reductions in degree of corneal opacity and inflammatory marker expression (TNF-α, IL-6, MMP-8, and MMP-9 mRNA) in all treatment groups

Table 2 continued

Study (year)	Design	Condition	Population (*n*)	Control arm	Frequency (duration)	Concomitant therapy	Results
Campos (2019) [44]	Multicenter, randomized, double-masked crossover clinical trial	Severe dry eye disease	Human (60)	Peripheral adult donor blood serum eye drops	8/day (1 month)	–	Corneal staining was more significantly reduced after the CBS treatment. Reduced VAS and OSDI scores were observed in both groups

UCBS umbilical cord blood serum, *NK* neurotrophic keratitis, *PED* persistent epithelial defect, *RCE* recurrent corneal erosion, *hAM* human amniotic membrane, *hPBS* human peripheral blood serum, *cGVHD* chronic graft-versus-host disease, *OSDI* Ocular Surface Disease Index, *VAS* Visual Analogue Scale, *ST* Schirmer's test, *TBUT* tear break-up time, *ED* epithelial defect, *LASEK* laser epithelial keratomileusis

standardized? How is the treatment used in terms of posology, treatment duration, and number of cycles [51]?

CONCLUSIONS AND FUTURE DIRECTIONS

Umbilical cord tissue is a major source of stem cells, which can be efficiently used to treat several ocular disorders. Therapeutic strategies based on stem cells depend not only on the synthesis of trophic and growth factors but also on the application of both mesenchymal and epithelial stem cells with anti-inflammatory and immune-privileged properties, as they can replace damaged tissues by differentiating into retinal and corneal epithelial, stromal, and endothelial cells. Several studies have evaluated the use of UCB in experimental models of induced retinal and corneal injuries, but there are still no data on its application in humans [52]. Further clinical studies are needed to evaluate the effect and long-term safety of this therapy in human ophthalmic disorders, to clarify pharmacokinetic aspects, and to provide a standardized therapeutic scheme for the clinical use of UCB. Future research should also focus on standardizing protocols for cell culture, differentiation, expansion, and cryopreservation, as well as optimizing cell culture media and scaffolds that can support cell proliferation, maintenance, and differentiation.

On the other hand, more robust evidence is available on the use of UCBS for the treatment of ocular surface diseases. In fact, various randomized clinical trials have been conducted in humans to not only assess UCBS efficacy and safety but also its clinical superiority to both autologous and allogeneic serum eye drops [28, 44]. However, there are still some aspects of the therapeutic use of UCBS that need to addressed in further clinical trials or laboratory analyses. For instance, clinical trials comparing autologous to allogeneic serum eye drops in terms of clinical efficacy and cost effectiveness are required. Detailed analyses of the constituents of allogeneic serum are required to investigate the biovariability among donations and the impact that this biovariability could

have on the effectiveness of the final product. Further research is also required on the optimal formulation (type of vehicle), dilution (20% vs 50–100%), duration of treatment (one or more months), and timing of repeated cycles (fixed or individualized for each clinical case). Last but not least, the development and validation of specific tools for both patient-reported and objective outcomes as well as minimal clinical datasets for collecting, analyzing, and sharing data are required.

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