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Autologous serum eye drops; Biological preparations; Dry eye disease; Ocular surface disorders; Platelet-rich plasma; Umbilical cord blood serum; Neurotrophic keratitis

Authors
Saud Ahmed Al-Shehri [1],
[1]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Abdullah Hamed Al-Maliki[2],
[2]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Mohammed Salem Bakhader[3],
[3]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Ali Ahmed Asiri [4],
[4]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Nawaf Mohammed Al-Zubali[5],
[5]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Abdulaziz Mohammed Al-Rashidi[6],
[6]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Abdullah Mohammed Salamah[7],
[7]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Abdulaziz Ali Al-Ghamdi [8],
[8]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Sultan Abdullah Al-Ghamdi[9],
[9] King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Mohammed Hamed Al-Maliki [10],
[10]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Haitham Mohammed Barnawi[11]
[11]King Abdulaziz University Hospital, Jeddah, Ministry of Education, Saudi Arabia.

Corresponding author: matawe@kau.edu.sa

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The Role of Biological Preparations in Treating Ocular Surface Disorders: A Literature Review

Abstract
The ocular surface disorders (OSDs) afflict the conjunctiva, the cornea, and the tear film, causing significant patient morbidity, visual impairment, and high costs of care. Historically, the treatment of OSDs has included artificial tears and anti-inflammatory medications. These methods provide only temporary symptomatic relief from signs/symptoms without necessarily addressing the underlying biological deficiency. Newer treatment modalities will be developed from biological products derived from deceased human beings. They will contain tissue-healing and regenerative factors present in the human tear film, i.e., growth factors, cytokines, and vitamins. We will conduct a literature search to provide a comprehensive overview of 65 studies published in peer-reviewed journals (2008-2025) that describe the efficacy, safety, and clinical use of autologous serum eye drops, allogeneic serum eye drops, PRP products, umbilical cord blood-derived products, topical insulin, and other biological preparations to treat corneal and/or ocular surface disease.

1. Introduction

Ocular surface disease involves many conditions that affect tear function, damage the surface of the eye, and cause inflammation. It can affect the cornea, conjunctiva and other structures. Ocular surface disease may be caused by Dry Eye Disease (DED), Persistent Corneal Epithelial Defects (PED's), Neurotrophic Keratitis (NK), Chemical Burns, and immunologically-mediated disorders such as Graft Versus Host Disease and Sjögren's. In the case of DED, the estimated global prevalence is 29.5%, making its burden on the health care system considerable.

Conventional methods of treatment include preservative-free artificial tears, anti-inflammatory medications applied to the eye and occlusion of the tear duct. These methods only relieve symptoms; they do not address the underlying biological conditions (Drew, 2018; Stępień, 2025). Biologically-based therapies include effective surgery, ocular surface lubrication, and ocular tissue regeneration, facilitated by bioactive materials found in healthy tears (Drew, 2018; Stępień, 2025).

Consequently, there is now an increase in the use of biologically based therapies under Blood-derived products for ocular surface disease due to the similarity in the composition of blood serum to that of natural tears (Cui et al., 2021; Drew et al., 2018; Higuchi, 2018). Both comprise growth factors, vitamins, immunoglobulins and other epitheliotrophic factors that stimulate the corneal epithelium and instigate wound healing (Cui et al., 2021; Drew et al., 2018; Higuchi, 2018; Stępień, 2025). The first to use serum as a treatment in chemical burns and chronic keratitis were Ralph et al. (1975), setting the foundations for the modern utilisation of biological therapy in ophthalmology (Drew et al., 2018; Nair et al., 2025).

We have tried in this review to summarise the recent evidence on the effectiveness, safety, and clinical applications of biological preparations for ocular surface disease, their pitfalls, and their future.

2. Methods: For this narrative literature review, we comprehensively

searched the databases of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for all published worksbetween 1 January 2008 and 31 March 2025. Allstudies selected for this synthesis addressed biologicalpreparations used to treat disorders affecting the ocularsurface; priority was given to those that were peer-reviewed original studies, systematic reviews, or meta-analyses containing data on clinical outcomes fromhuman subjects. A total of 65 publications met theabove criteria to be included in this synthesis.The inclusion criteria were as follows: (1) peer-reviewed original research, systematic reviews, meta-analyses, and expert consensus guidelines; (2) studiesreporting clinical outcomes in human subjects; (3) invitro or translational studies with direct clinicalrelevance; and (4) publications in English. Theexclusion criteria were as follows: (1) case reportswith fewer than five patients, unless describing uniqueclinical phenomena; (2) conference abstracts withoutfull peer-reviewed publications; and (3) studies with insufficient methodological reporting. In total, 65 peer-reviewed publications met the inclusion criteria

3. Autologous Serum Eye Drops

3.1 Composition and Mechanism of Action

Autologous serum drops are prepared from the patient's blood. They have a physiological combination of biomolecules that resemble those found in the body (Cui et al., 2021; Higuchi, 2018; Stępień, 2025). These have different types of therapeutic effect due to the presence of different types of growth factors like; Epidermal Growth Factor (EGF), Transforming Growth Factor - beta (TGF-β), Platelet-Derived Growth Factor (PDGF), Insulin-like Growth Factor - 1 (IGF-1) and Nerve Growth Factor (NGF) (Cui et al., 2021, Na & Kim, 2012, Higuchi, 2018 and Nair et al., 2025). Other active components found in serum include fibronectin, which helps with epithelial cell adhesion and migration, and Vitamins A and E, which help with epithelial differentiation and provide antioxidant properties (Cui et al., 2021; Higuchi, 2018; Stępień, 2025).

Biochemical similarities noted between serum and tears provide the basis of ASED therapy (Cui et al., 2021; Drew et al., 2018; Higuchi, 2018). Higuchi (2018) has shown that serum components, to a degree, mimic tear constituents, thereby improving the dry eye effects of ASDEs by supplementing the ocular surface with essential factors. Further, immunoglobulins and antimicrobial factors in the serum provide other benefits. (Cui et al., 2021; Stępień, 2025).

3.2 Clinical Efficacy in Dry Eye Disease

The effects of ASEDs on the clinical management of dry eye disease have been studied (though not necessarily producing high-quality evidence) (Cui et al., 2021; Higuchi, 2018; Pan et al., 2013; Quan et al., 2023). One study reported ASEDs to be well tolerated, while citing positive "possible associated" effects on patient-reported outcomes, as well as objective dry eye parameters (Cui et al., 2021). It has been theorised that the increased concentrations of growth factors, electrolytes, antioxidants, and immunoglobulins explain how serum eye drops promote maintenance and healing of the ocular surface (Cui et al., 2021).

Systematic reviews have attempted to pool the evidence base for ASEDs' efficacy. Pan et al. (2013) conducted a Cochrane systematic review comparing the effects of ASEDs with artificial tears, finding low-certainty evidence of symptom improvement at 2 weeks with ASED use. Still, the duration of the effect was therefore unclear in the longer term. The quality of evidence from randomised controlled trials was rated low (Pan et al., 2013) - and similarly, Quan et al. (2023) completed an updated systematic review of six randomised clinical trials involving 116 participants and summarised that, while symptoms did improve marginally compared to artificial tears for 2 weeks, ASED effectiveness remains uncertain at this time based on the current data.

Despite these constraints, the use of ‘apheresis’ techniques in clinical settings has proved advantageous for the management of aqueous deficiency (refractory to other means) in patients with dry eye disease (Cui et al., 2021; Lee & Chen, 2008; Uçakhan et al., 2023). Based on their analysis of long-term outcomes, using ASED to treat patients suffering from severe dry eye syndrome was effective, as they had noted improvements in corneal fluorescein staining and required fewer topicals for lubrication based on the evidence gathered (Lee & Chen,2008). (García-Martín et al., 2018) reports that, except for one patient out of 173 patients treated with ASEDs for a variety of ocular surface disorders, every patient reported an improvement in symptoms with no adverse events associated.

3.3 Applications in Persistent Epithelial Defects and Neurotrophic Keratitis

The use of ASEDs has shown effectiveness in treating long-standing corneal epithelial defects and neurotrophic keratitis (Janićijević-Petrović; Font & Cortina; Kim et al.; Lekhanont et al.). ASED therapy used on 116 eyes with corneal defects from post-chemical injuries showed that these patients had a healing rate of 48.28% within the first 4 weeks after starting the ASED therapy. This was a significant decrease in time to healing compared with traditional methods of repairing these eyes.

According to research conducted by Lekhanont et al. (2016), use of 100% undiluted serum eye drops was noted to be successful in treating PEDs (87.16%) versus conventional treatments (69.62%). In addition, the researchers noted that the median time to full epithelisation was significantly different between the two study groups at 14 days (serum treatment group) and 28 days (conventional treatment group). Therefore, these findings would indicate that using higher concentrations of serum provides superior therapeutic benefit.

For neurotrophic keratitis, Font and Cortina (2025) reported that “autologous blood-derived products such as ASEDs, platelet-rich plasma, and plasma rich in growth factors have proved effective for treating PEDs and NK through the delivery of neurotrophic factors indispensable for corneal physiology.” In a different

application of autologous serum, Kim et al. (2022) applied autologous serum gel for neurotrophic PEDs related to lagophthalmos and attained epithelial healing within 2 to 8 weeks.

3.4 Applications in Graft-Versus-Host Disease

Ocular GVHD is an especially intractable variant of systemic GVHD following allogeneic haematopoietic stem cell transplantation, characterised by conjunctival inflammation and dry eye (Na & Kim, 2012; Ogawa et al., 2003; Altan-Yaycıoğlu et al., 2022). The potential use of ASEDs in treating ASEDs in those with chronic GVHD affecting the eyes was examined by Ogawa et al. (2003), who showed that topical serum treatment appears safe and effective, possibly acting as a topical immunosuppressant in patients on systemic immunosuppressive therapy.

Kim and Na (2012) studied 16 patients suffering from long-term dry eyes due to chronic graft vs host disease and compared their allogenic serum drops to other treatments over 4 weeks. The patients' symptom scores, break-up time, corneal staining and goblet cell counts improved after the first 4 weeks of treatment. In the study by Altan-Yaycıoğlu et al. (2022) 80% of patients were treated with either autologous or allogeneic eye drops and all presented improvement of clinical signs as well as visual acuity after 6 months of treatment for ocular graft vs host disease.

3.5 Other Clinical Applications

ASEDs are also effective for treating other ocular surface diseases. A recent article by Lin et al. (2015) documented the successful use of 20% ASEDs for treating patients who had chronic LASIK-induced neurotrophic epitheliopathy and demonstrated a complete resolution of symptoms. Semeraro et al. (2014) explored the use of 50% ASEDs in acute conditions (chemical burns) and chronic pathologies (recurrent corneal erosion, neurotrophic keratitis, keratoconjunctivitis sicca). They concluded that all epithelial defects were healed.

Abedi and Hamrah (2018) reported a case of acute ultraviolet keratitis treated with autologous serum eye drops (ASEDs) in which dramatic recovery of subbasal corneal nerves was seen on in vivo confocal microscopy. This case highlights the rationale for the neurotrophic potential of serum-derived growth factors in promoting corneal nerve recovery (Abedi & Hamrah, 2018).

3.6 Preparation and Standardization Challenges

Despite their extensive clinical use, there is considerable diversity in the preparation of ASEDs, making it difficult to standardise treatments and compare results from studies (Cui et al., 2021; Pan et al., 2013; Marks & Meer, 2017). Marks and Meer (2017) conducted a global survey. They concluded that "these results indicate significant divergence in the methods used to prepare autologous serum drops, although the majority produced small volume aliquots for self-administration by patients".

Clinically used concentrations range from 20% to 100%, using normal saline or sodium hyaluronate as diluents (Cui et al., 2021; Pan et al., 2013; Rauz et al., 2017). The Royal College of Ophthalmologists (Rauz et al., 2017) guidelines suggest acceptable concentration and use of ASEDs, even if published data show similarities between the constituents of the tears and serum that negotiate an underlying rationale for their therapy - how concentrated they can be, however, remains debatable, though, some suggest that the greater the concentration (from 50%–100%) the greater the therapeutic benefits (Lekhanont et al., 2016; Semeraro et al., 2014).

Logistical hurdles also affect storage requirements. ASEDs must be stored frozen (<−18°C), and thawed drops must be used within a limited timeframe to prevent instability and contamination (Cui et al., 2021; Antoniewicz-Papis, 2021; Latham et al., 2023). Latham et al. (2023) presented some environmental impacts concerning the production and distribution of ASEDs; overall, the authors concluded that “current procedures exist in the UK that are adequate to ensure the safety and efficacy of ASEDs while not compromising the ability to donate frequently.

4. Allogeneic Serum Eye Drops

4.1 Rationale and Advantages

Allogeneic serum eye drops (allo-SEDs) from healthy blood donors present another option where patients are unable to provide usable blood donations (Cui et al., 2021; Na and Kim, 2012; Meer et al., 2021). Cui et al. (2021) comment that the limitations of accessibility that reduce patient use of autologous serum, such as logistical and financial burden, may be met by the use of allogeneic preparations. Recent studies have shown that these drops are safe and effective and of benefit to patients relative to SEDs (Cui et al., 2021; Meer et al., 2021).

The advantages of allogeneic sources include the potential to obtain greater quantities from a single donor, production standardization and batch release from healthy persons, and the ability to supply patients who have contraindications to donating their own blood, for example, patients with anemia, systemic inflammation or pediatric patients (Cui et al., 2021; Giannaccare et al., 2020; Giannaccare et al., 2022). Gabriel et al. (2023) have coined the term “eye drops of human origin” (EDHO) to portray that these products are similar to medical products of human origin in terms of their wide variety of sources and clinical uses.

4.2 Clinical Evidence

A prospective, double-blind, crossover trial compared autologous SEDs and allogeneic ones in severe dry eye patients, with similar efficacy and tolerability between the two preparations, and a comparable improvement in Ocular Surface Disease Index in both (Meer et al., 2021). All mild adverse events were completely resolved. Allo-SEDs may be an attractive alternative for individuals who are unable to donate blood (Meer et al., 2021).

Na and Kim (2012) addressed the use of allogeneic serum from unrelated healthy donors for the treatment of dry eye in patients with chronic GVHD and

demonstrated improvement in several clinical parameters for these patients. The authors indicated that allogeneic serum represents a good alternative when autologous serum is not available due to patients' ideas about venipuncture and concerns about the risk of infection (Na & Kim, 2012).

Vermeulen et al. (2023) performed a randomised clinical trial of micro-(7 µL) versus conventional-volume (50 µL) allogeneic SEDs and reported the non-inferiority of the micro-drops. Both volumes had similar clinical performance, estimated by OSDI scores, and both drops also significantly increased tear break-up time and corneal punctate lesions assessed by slit-lamp examination (Vermeulen et al., 2023). This is particularly useful for conserving valuable donor serum.

4.3 Safety Considerations

While these allogeneic preparations are convenient, they harbour the potential threat of causing hypersensitivity reactions and transmission of blood-borne diseases (Quan et al., 2023; Meer et al., 2021). Quan et al. (2023) mentioned that "due to infectious and immunologic safety issues, using autologous serum instead of allogenic serum is preferred when possible." However, rigorous screening protocols for donors and eliminating the use of donors that screen positive for infectious agents by quarantine-type methods mitigate this risk (Meer et al., 2021).

Gabriel et al. Gabriel et al. (2023) noted that 'Harmonized quality and production standards are needed for EDHO, as there is wide variability in the manufacture between institutions' and all agreed that allogeneic EDHOs have advantages over autologous preparations, although more data on clinical efficacy and safety are required (Gabriel et al., 2023).

5. Platelet-Rich Plasma and Related Products

5.1 Composition and Preparation

An advancement of blood-based ocular treatment has been brought forth by the introduction of preparations made from platelet-rich plasma (PRP) and its equivalents, where they contain much higher concentrations of growth factors than serum (Stępień, 2025; Nair et al., 2025; Lee et al., 2016). According to Nair et al (2025), the three main types of autologous blood-derived platelet preparations for the treatment of ocular surface diseases are PRP, plasma rich in growth factors (PRGF) and platelet lysate, which differ from each other according to how many platelets were present in the preparation, and how they were prepared.

PRP (platelet-rich plasma) is produced using whole blood, which means using whole blood to separate and concentrate platelets from one another. This increases platelet density in the PRP and subsequently increases the concentration of platelet-derived growth factor (PDGF), transforming growth factor (TGF) β, vascular endothelial growth factor (VEGF), and all the other bioactive compounds (Stępień, 2025; Nair et al., 2025; Lee et al., 2016). PDGF is the major contributor to the wound-healing benefits attributed to PRP because it is responsible for starting tissue regeneration and stimulating angiogenesis (Anam et al, 2024). PDGF and other growth factors can also be attained through freeze-thawing PC or from other, purer sources to create a "platelet lysate." This causes the intracellular content of the platelets to be released (e.g., autologous conditioned serum) (Stępień, 2025; Antoniewicz-Papis, 2021).

5.2 Clinical Applications

Lee et al. (2016) retrospectively assessed the effect of autologous PRP eye drops in the context of recurrent corneal erosions by comparing 27 patients treated with PRP eye drops with 20 patients treated with lubricant therapy. Patients treated with PRP showed lower rates of recurrence (22.2% major recurrent versus 80.0% controls) and lower recurrence rate (0.06 versus 0.39 per month) (Lee et al. 2016). No side effect was noted at follow-up.

The differences that Jongkhajornpong et al. (2024) found when comparing the concentrations of epitheliotrophic factor levels in both undiluted autologous PRP and autologous serum would suggest that PRP contains higher concentrations of EGF, basic fibroblast growth factor (bFGF), and β-NGF, whilst serum yields HGF, PDGF-AA, PDGF-BB, and VEGF - capable of "modifying and adjusting treatments according to the underlying pathophysiology."

In a later RCT, Jongkhajornpong et al. (2024) compared 100% autologous PRP vs. 100% autologous serum in 96 moderate-to-severe patients with DED (assessed using OSDI and TBUT): "100% autologous PRP was not inferior to 100% autologous serum in reducing dry eye symptoms and ocular surface staining at four weeks, with no differences between treatment groups for the secondary outcomes"

5.3 Plasma Rich in Growth Factors (PRGF)

PRGF-Endoret is a platelet-derived product that has been standardized for use in ophthalmology (Ghalibafan et al., 2023; Sánchez-Ávila et al., 2018; Sanchez-Avila et al., 2017). (Ghalibafan et al., 2023) evaluated the effect of PRGF eye drops in stage 1 neurotrophic keratitis and reported significant improvements in corneal sensitivity, tear break-up time, Schirmer scores and corneal staining in treated eyes. The authors emphasised that PRGF would be an effective and safe alternative therapy for the onset and advanced stages of NK.

A total of twelve patients were involved in a retrospective trial of the use of immunosafe PRGF eye drops in chronic ocular GVHD. Statistically significant corneal staining area (75.7 % versus baseline), visual acuity (74.7 % versus baseline) and symptom scores (Sánchez-Ávila et al., 2018). Corneas were stabilized without risk of perforation, and no adverse events were observed (Sánchez-Ávila et al., 2018).

In a study by Sánchez-Ávila et al. (2017), it was shown that PRGF-Endoret eye drops reduced signs and symptoms of dry eye in patients with primary and secondary Sjögren's syndrome, suggesting that the treatment was safe and effective for these difficult-to-treat patients.

5.4 Comparative Studies

Recent comparative studies have tried to establish the superiority of one technique over the other for producing various types of platelet derivatives.

Manohar and Shtein (2023) point out that a small clinical trial compared autologous serum with PRP and found no difference in patient preference or clinical outcomes between the two, but there were differences in epitheliotropic factors concentrations.

Anitua et al. (2021) performed a proteomic characterisation of PRGF vs undiluted autologous serum, finding that undiluted serum activated inflammatory, angiogenic, oxidative stress and scarring pathways in human corneal keratocytes. Thus, suggesting that PRGF could be a better alternative to serum for treating ocular surface disorders.

6. Umbilical Cord Blood Products

6.1 Rationale and Composition

Ocular surface therapy products derived from umbilical cord blood (UCB) and its derivatives represent a potentially effective alternative to peripheral blood-based products. (Foti et al., 2024; Giannaccare et al., 2020; Wong et al., 2023). Giannaccare et al. (2020) attempted a systematic review and noted that cord blood serum products have higher concentrations of biologically active components and growth factors than serum obtained from adult peripheral blood.

Advantages of products derived from UCB are related to the collection of larger amounts from one donation, therapeutic convenience in patients with poor general condition or blood dyscrasias and possibly better effector growth factors (Giannaccare et al; Wong et al). Foti et al. (2024) show HUCBs accelerate corneal epithelial repair and preserve the integrity of ocular surface epithelium through its anti-inflammatory activity.

6.2 Clinical Evidence

In a study conducted by Wong et al (2023), they evaluated umbilical cord plasma eye drops on 40 Singaporeans suffering from refractory dry eye disease. The findings of their study showed that the mean keratoepitheliopathy staining score was significantly reduced, as well as an improvement in tear break-up time and symptom scores from baseline to post-treatment in the experimental group. Therefore, the authors believe that umbilical cord plasma eye drops are a novel treatment option for those patients who suffer from refractory dry eye disease.

Foti et al. (2024) performed a prospective study of HUCBS in 49 patients with severe ocular surface disorders resistant to conventional treatment, including Sjögren's syndrome, GVHD, neurotrophic ulcers and Stevens–Johnson syndrome. This study observed statistically significant improvements in symptom questionnaires, Schirmer test, tear break-up time, visual acuity and corneal staining scores.

Comparative studies have suggested advantages of UCB relative to autologous serum. Giannaccare et al. (2020) suggested that "the ubiquitous accessible human umbilical cord serum can exert superior effects over autologous serum in some studies, with a trend towards improved symptom scores and keratoepitheliopathy in patients with severe dry eyes. Wong et al. (2023) reported better improvement in patients treated with cord serum compared to patients treated with autologous serum for persistent corneal epithelial defects.

6.3 Pediatric Applications

UCB-derived products have the additional advantage for children in conditions where it is difficult to retrieve their own (autologous) blood samples (Giannaccare et al., 2020; Giannaccare et al., 2022). Maternal serum eye drops have proven effective in the treatment of bilateral neurotrophic keratopathy (Giannaccare et al., 2022). This indicates that when an autologous source is unfeasible, an allogenic source (maternal serum in this instance) can be used to derive a product with similar results.

7. Emerging Biological Therapies

7.1 Topical Insulin

Topical insulin as a new biological therapy for corneal epithelial regeneration (Burgos-Blasco et al., 2023; Giannaccare et al., 2023; Radulescu et al., 2024; Scripcă et al., 2025; Díaz-Valle et al., 2021). (Burgos-Blasco et al., 2023) tested this novel topical "eye drops" delivered insulin on a dry eye disease model and showed significant improvement in corneal staining and symptoms after three-month treatment with insulin eye drops with no adverse events.

Díaz-Valle et al. (2021) compared retrospectively a cohort of patients receiving topical insulin with a cohort receiving autologous serum for persistent epithelial defects. They found that epithelialisation was achieved in 84% of the insulin-treated patients compared with 48% of the autologous serum-treated patients. The mean time to re-epithelialisation was significantly shorter with insulin (32.6 days vs. 82.6 days), and the need for amniotic membrane transplantation was significantly lower.

Scripcă et al. (2025) reviewed the use of topical insulin in neurotrophic keratopathy, finding that a regimen of topical insulin was an inexpensive and safe treatment associated with improved safety and outcomes for corneal epithelial regeneration. The authors report that "Compared with existing traditional treatments, such as autologous serum, insulin eye drops represent a ready-to-use and cheap alternative with the possibility of easy implementation under the advice of any physician familiar with diabetes mellitus".

7.2 Recombinant Growth Factors

As a biological treatment for neurotrophic keratitis, recombinant human nerve growth factor (rhNGF, cenegermin) is an important innovation (Font & Cortina, 2025; Chen et al., 2022). In a review by Font and Cortina (2025), they found that cenegermin is effective in the treatment of NK, but its use has only been approved and funded in patients ≥ 18 years of age. (EGF) eye drops Lou-Bonafonte et al. (2012) performed a meta-analysis of EGF eye drops. Their findings demonstrated 86.8% clinical efficacy for the treatment of acute heterogeneous cornea condition and identified no considerable risks of adverse events associated with the use of EGF eye drops. The authors

concluded that EGF eye drops may help promote healing following refractive surgery, and may be of benefit in the treatment of various cornea conditions (Lou-Bonafonte et al., 2012)..

7.3 Amniotic Membrane Products

Blood-derived products and amniotic membrane, as well as their derivatives, share properties for both anti-inflammation and regeneration. According to Nair et al. (2025), amniotic membrane extracts and human amniotic fluid eye drops are new additions to the biological therapy toolkit when treating ocular surface conditions. (Stępień, 2025; Nair et al., 2025).

8. Comparative Efficacy and Treatment Selection

8.1 Blood-Derived Products Comparison

Because the number of biological products available to treat DED is expanding, additional comparative studies are being performed to assist clinicians in making decisions regarding the use of these products. Mederle and his associates conducted a systematic review and meta-analysis to analyze the effects of PRP, autologous serum and artificial tears on DED (Mederle et al 2025). PRP and autologous serum were shown to produce statistically greater improvements in OSDI scores, TBUT and Schirmer scores than artificial tears; additionally, there were tendencies for PRP to perform better than autologous serum (Mederle et al 2025).

(Bernabei et al,2019) developed the "5 Ws and 2 Hs" protocol for blood-derived eye drops that describes who is to be treated, what the rationale for treatment is, when to begin therapy, where therapy is to occur, how to prepare for therapy and how to administer the reagent. The authors state that allogeneic sources are becoming increasingly innovative in populating the growing industry of custom-made eye drops developed specifically for a particular type of patient and/or ocular surface disease.

8.2 Disease-Specific Considerations

The type of ocular surface disorder being treated should dictate treatment choice. Autologous serum and PRP appear to be effective in this regard for dry eye disease, although the quality of evidence is poor (Cui et al., 2021; Quan et al., 2023; Jongkhajornpong et al., 2024). For persistent epithelial defects higher serum concentrations (50–100%) and PRP would presumably be more beneficial (Lekhanont et al., 2016; Semeraro et al., 2014; Jongkhajornpong et al., 2024).

PRGF has shown some potential (Ghalibafan et al., 2023; Sánchez-Ávila et al., 2018), whereas topical insulin is a novel and inexpensive alternative (Scripcă et al., 2025; Díaz-Valle et al., 2021).. Both autologous and allogeneic serum preparations have demonstrated efficacy (Na & Kim, 2012; Ogawa et al., 2003; Altan-Yaycıoğlu et al., 2022; Sánchez-Ávila et al., 2018).

9. Safety Considerations and Adverse Events

9.1 General Safety Profile

There have been multiple studies indicating that blood-derived eye drops have shown very good safety. According to Cui et al. (2021), patients have tolerated ASEDs (autologous serum eye drops) very well, and in a study by García-Martín et al. (2018), not one of 173 patients treated with ASEDs demonstrated any harmful effects after receiving ASED treatment for a long period of time.

The authors Nair et al (2008) summarise the risks, i.e., adverse (bad) events with the use of autologous (self) serum (such as the rare instances of reported contamination and reports of the body's immune systems reacting to the injection). However, in the event that the proper storage and preparation of the autologous serum is undertaken, the rate of serious adverse events will be uncommon compared to rates of serious adverse events (by Nair et al., 2008; Rauz et al., 2017).

9.2 Contamination Risks

The main safety risk associated with blood-derived eye drops is microbial contamination (Cui et al., 2021; Lee & Chen, 2008; Kirwan et al., 2023). In Lee & Chen's (2008) view, consideration must be given to contamination to the least extent practicable to reduce the risk of infection. As Kirwan et al. (2023) describe, they applied a fully closed manufacturing process to serum eye drops, thereby precluding bacterial contamination and improving patient safety.

Storage specifications are important to RNG and to ensuring the sterility and stability of the product (Cui et al., 2021; Antoniewicz-Papis, 2021; Latham et al., 2023). For example, eye drops need to be stored frozen and used within a few days after thawing, or given a very short timeframe to use them or discard them (Cui et al., 2021; Latham et al., 2023).

10. Limitations and Future Directions

10.1 Current Limitations

Despite the encouraging results, the evidence for these biological preparations is tempered by several limitations. Foremost among these is the challenge of standardising preparation protocols as the concentrations of the preparation, diluent and storage conditions vary widely between institutions (Cui et al., 2021; Stępień, 2025; Pan et al., 2013; Marks & Meer, 2017).

The quality of evidence overall derived from randomised controlled trials is found to be only modest, especially for long-term outcomes (Cui et al., 2021; Pan et al., 2013; Quan et al., 2023). The latter pointedly noted that high-quality large trials enrolling participants with a diverse range of severities and the development of core outcome sets would be helpful to enable truly evidence-based treatment decisions.

Although potentially inexpensive, cost and accessibility are other barriers to widespread use (Cui et al., 2021; Stępień, 2025; Manohar & Shtein, 2023). Blood-derived eye drops need production in specialized facilities with trained personnel, limiting access (Pan et al., 2013; Manohar & Shtein, 2023).

10.2 Future Directions

Stępień (2025) presented the current status and future research directions in relation to the research of PRP, which included standardising the PRP preparation protocols, developing future generation platelet concentrates, and using multi-omic technologies to

fully characterise both the biomechanical and the therapeutic activities.

In their research, Gabriel et al. (2023) worked to reinforce the need for an alignment of standards and guidance regarding emergency drug health care online (EDHO). The standardisation should be carried out for depository preparations (allogeneic) since this type of preparation not only aids easy manufacturing but also affords some commonality of manufacturer by pooling (and thereby an exertion of) a common minimal standard of manufacturer consistency. They were also able to ascertain that the manufacture and elaboration of lyophilized serum-based eye drop formulations might be a paradigm that will increase the lifetime of the product and reduce the environmental burden of EDHO products (Latham et al., 2023).

Future directions of research involve testing of products like topical insulin, recombinant growth factors, and biological agents from platelets (Burgos-Blasco et al. 2023; Scripcă et al. 2025; Lou-Bonafonte et al. 2012). Our recommendations for future research should be to focus on the assessment of these new horizons therapeutics using comparative and predictive biomarkers ("Use it or lose it"). Therapy should ultimately be more or less tailored to individuals based on which pathophysiological processes manifest (Stępień, 2025; Bernabei et al., 2019; Jongkhajornpong et al., 2024).

11. Conclusions

Biological preparations have emerged as a significant step forward in treating ocular surface diseases, providing a wide variety of therapeutic options that go beyond symptomatic relief, such as conventional artificial tears and anti-inflammatory medicines. Within this category, autologous serum eye drops have been studied the most and have consistently demonstrated clinical benefit in a range of clinical conditions, including dry eye disease, persistent corneal epithelial defects, neurotrophic keratitis, and ocular graft versus host disease. Allogeneic serum preparations also provide comparative efficacy and an acceptable safety profile when autologous donation is not possible, thereby expanding patient access to this type of therapy.

Blood-derived ocular therapies have advanced into a new level of complexity with the introduction of PRP and its derivatives, which allow for greater availability of EGF than previously achieved by just using blood alone. These products have shown promise for the treatment of recurrent corneal erosion and neurotrophic corneas. At this time, umbilical cord blood products may provide an even better alternative to blood-derived therapies by providing bioactive substances. Additionally, new therapies such as topical insulin and recombinant growth factors are contributing to the expanded therapeutic options and may be more cost-effective than traditional treatments. It is important to note that many of the new and emerging treatments can be used in clinical environments that lack adequate resources.

Even though progress is being made, there are still a number of major issues that must be addressed. Protocols for preparation vary greatly from setting to setting; quality of evidence from randomised controlled trials tends to be medium to low; and long-term outcome data are sparse or nonexistent. To address these gaps, a major effort is needed toward establishing harmonised standards of manufacture, conducting large-scale randomised trials comparing effectiveness, and developing validated core outcome sets. Optimising patient outcomes is likely to take place based upon an individual's biological therapy being tailored to them, and directed by the underlying pathophysiological mechanism of their particular ocular surface disease.

12. References

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