







REPORT

Eye drops of human origin—Current status and future needs: Report on the workshop organized by the ISBT Working Party for Cellular Therapies

Christian Gabriel^{1,2}  | Denese C. Marks^{3,4}  | Reinhard Henschler⁵  |
Katharina Schallmoser^{6,7}  | Thierry Burnouf^{8,9}  | Mickey B. C. Koh¹⁰ 

¹Department of Blood Group Serology and Transfusion Medicine, Medical University of Graz, Graz, Austria

²Ludwig Boltzmann Institute for Clinical and Experimental Traumatology, Vienna, Austria

³Research and Development, The Australian Red Cross Lifeblood, Sydney, Australia

⁴Sydney Medical School, The University of Sydney, Sydney, Australia

⁵Institute of Transfusion Medicine, University Hospital and Medical Faculty, University of Leipzig, Leipzig, Germany

⁶Spinal Cord Injury and Tissue Regeneration Center Salzburg (SCI-TReCS), Paracelsus Medical University (PMU), Salzburg, Austria

⁷Department of Blood Group Serology and Transfusion Medicine, Universitätsklinikum, Salzburger Landeskliniken GesmbH (SALK), Salzburg, Austria

⁸Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan

⁹International PhD Program in Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan

¹⁰Institute for Infection and Immunity, St. George's University of London, Cranmer Terrace, Jenner Wing, London, UK

Correspondence

Mickey B. C. Koh, Institute for Infection and Immunity, St. George's University of London, Cranmer Terrace, Jenner Wing, Corridor 6, London SW17 0QT, UK.
Email: mickey.koh@stgeorges.nhs.uk

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Abstract

Background and Objectives: Serum eye drops (SEDs) are used to treat ocular surface disease (OSD) and to promote ocular surface renewal. However, their use and production are not standardized, and several new forms of human eye drops have been developed.

Materials and Methods: The International Society for Blood Transfusion Working Party (ISBT WP) for Cellular Therapies held a workshop to review the current types of eye drops of human origin (EDHO) status and provide guidance.

Results: The ISBT WP for Cellular Therapies introduced the new terminology 'EDHO' to emphasize that these products are analogous to 'medical products of human origin'. This concept encompasses their source (serum, platelet lysate, and cord blood) and the increasingly diverse spectrum of clinical usage in ophthalmology and the need for traceability. The workshop identified the wide variability in EDHO manufacturing, lack of harmonized quality and production standards, distribution issues, reimbursement schemes and regulations. EDHO use and efficacy is established for the treatment of OSD, especially for those refractory to conventional treatments.

Conclusion: Production and distribution of single-donor donations are cumbersome and complex. The workshop participants agreed that allogeneic EDHO have

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advantages over autologous EDHO although more data on clinical efficacy and safety are needed. Allogeneic EDHOs enable more efficient production and, when pooled, can provide enhanced standardization for clinical consistency, provided optimal margin of virus safety is ensured. Newer products, including platelet-lysate- and cord-blood-derived EDHO, show promise and benefits over SED, but their safety and efficacy are yet to be fully established. This workshop highlighted the need for harmonization of EDHO standards and guidelines.

Keywords

eye drops of human origin, ocular surface disease, serum eye drops

Highlights

- All eye drops of human origin (EDHO) are classified as medical products of human origin and therefore should have strict oversight with regards to donor eligibility, infectious disease transmission prevention, consistent labelling and traceability. Currently, production, quality indicators and regulatory oversight for EDHO differ among jurisdictions.
- Allogeneic EDHO should be explored as an alternative to autologous EDHO due to greater standardization and consistency.
- High-level evidence (randomized clinical trials) for the use of EDHO remains a priority, especially for allogeneic EDHOs, while reasonable evidence for efficacy of autologous EDHO in the treatment of ocular surface disease refractory to conventional treatment exists.

INTRODUCTION

A 3-day workshop on eye drops of human origin (EDHO), organized by the International Society for Blood Transfusion Working Party (ISBT WP) for Cellular Therapies, was held in Vienna in May 2022. The intention was to provide a discussion forum on the current use of EDHO. The meeting included all major stakeholders in the field including researchers, scientists, clinicians, blood bankers and regulatory authorities. The workshop covered all relevant aspects of EDHO including basic science of the anterior eye, diseases that would benefit from EDHO, autologous versus allogeneic donation, production, quality and safety indicators and regulatory oversight.

BASICS OF THE ANTERIOR EYE, SERUM AND PLATELETS

In the opening lecture, Denese Marks (Sydney, Australia) presented an overview of a BEST survey on serum eye drops (SEDs) [1]. Responses were received from 12 countries and from 21 centres producing SED in countries with a high development index, with the majority from the United States and Europe. At the time of the survey, the majority of centres were producing autologous SED (70%), and this has likely changed. The survey also highlighted the wide inter-centre variations in blood collection volumes, serum dilution ratios, frozen and thawed shelf-life and infectious disease screening of donors. There is a high level of variation from the resources and established methods in each centre.

Friedrich Paulsen (Erlangen, Germany) described the anatomy, functional interplay of lacrimal glands, meibomian glands and the

cornea [2]. Tears developed more than 300 million years ago in first terrestrial organisms leaving the aquatic environment and contain more than 1500 antimicrobial proteins, including lactoferrin, IgA and lipocalin [3]. The human tear film has three layers serving different functions [4]. Aside from the main lacrimal glands, there are many smaller glands in the eyelid producing lipids and mucous components. Of particular importance are meibomian glands, which produce highly hydrophobic waxes or steryl-ester lipids in the outermost layer of the tear film, reducing evaporation of tears, retarding tear overflow and enhancing stability of the tear film [5].

Sonja Mertsch (Oldenburg, Germany) discussed the current research to produce and regenerate lacrimal glands. Murine epithelial progenitor cells can be expanded to small aggregates of acinar and ductal components [6]. When transplanted, these tissue-engineered products reduce inflammation and improve tear production in animal models. Different types of mesenchymal stromal cells (MSCs) have also been tested for lacrimal gland regeneration [7]. It appears that bone-marrow- and adipose-derived MSC showed better regenerative capacity than MSC from lacrimal glands [8, 9]. Bio-engineered lacrimal glands, in which MSC, primary epithelial cells and endothelial cells are co-cultivated to form spheres in a vascularized scaffold are showing initial promising results, although the road remains long for translation into clinical practice.

Reinhard Henschler (Leipzig, Germany) reported on the content of human serum and plasma, with a focus on differences to healthy human tears. Serum or plasma have a water content of up to 95 and a specific density of 1.022–1.026, and its pH and osmolarity similar to human tears [10]. Specific differences between serum and plasma are few, with serotonin, a higher nucleoside content and absence of

fibrinogen in serum being hallmarks. Circadian rhythms influence serum and plasma content of some factors including hormones (e.g., cortisol), tumour necrosis factor- α and interleukin-6. About 600 different lipids are found in serum, some of which have immunoregulatory properties and thus are likely to be important for EDHO activity [11]. Microbicidal proteins and peptides in serum include β -defensins, cathelicidin (LL-37), lysozyme, neutrophil peptides, lactoferrin and thrombin fragments, all of interest for EDHO [12, 13]. Among cytokines, the concentration of epidermal growth factor (EGF), transforming growth factor- α and - β , platelet-derived growth factor, nerve growth factor, insulin-like growth factor and hepatocyte growth factor are in a comparable order of magnitude equal in serum and in tears. Extracellular vesicles (EVs) are also found in serum and may play a role in transferring micro-RNAs even in tears [14]. Cell-free DNA in serum may be a relevant constituent of EDHO since it encodes pro-inflammatory signals [15]. In conclusion, EDHO are complex and have only been partially characterized, with some candidate effectors mirroring that of human tear.

Thierry Burnouf (Taipei, Taiwan) showed that platelets contain approximately 5000 proteins derived from megakaryocytes or internalized from the blood circulation through their open canalicular system. α -granules are particularly rich in growth and other trophic factors [16]. Platelets can release regenerative growth factors through degranulation or within extracellular vesicles (EVs), which may be internalized via receptors from other cells. Platelet concentrates can be subjected to freeze-thaw cycles to produce a lysate containing plasma and platelet components [17]. Fibrinogen from the plasma fraction can be depleted by sero-conversion to generate EDHO. As platelet lysate is rich in growth factors and antioxidants, it can protect corneal epithelial cells from oxidative stress and apoptosis, enhancing their viability [18].

Take-home points:

1. Significant inter-centre variations exist in blood collection volumes, serum dilution ratios, frozen and thawed shelf-life and infectious disease screening of donors in the production of SEDs
2. Plasma, serum and platelet lysates contain trophic factors, (protective) lipids and several microbicidal peptides similar to human tears. The factors most critical for determining the efficacy of EDHO and at what therapeutic levels are yet to be fully characterized.
3. There is promise and ongoing research looking at regeneration of lacrimal glands including the early use of MSCs in murine models.

OCULAR SURFACE DISEASE

Dry eye disease (DED) and Sjögren's syndrome (SS) with ocular involvement are examples of ocular surface disease (OSD) treated with SED. Jutta Horwath Winter (Graz, Austria) revealed that up to 35% of the population might be affected, depending on the definition of DED, diagnostic testing and awareness. The prevalence of DED rises above the age of 50, and more recently, the prevalence in younger populations has increased due to the use of smartphones and computers [19]. In DED, visual acuity is impacted by the reduction of tear production,

whereby the instability of the tear film leads to surface alterations and scarring [20, 21]. Diagnostic tear film testing allows the classification into decreased lacrimal gland production (with or without Sjögren's syndrome) and increased evaporation [22, 23]. SS is characterized by DED and dry mouth (with severe deficiency of the lacrimal glands and secondary detrimental effects of the meibomian glands). It requires a staged management, in which SED are recommended [24, 25].

Treatment of ocular graft-versus-host disease (GVHD), a systemic disease occurring after stem cell transplantation, is the second most common condition for which SED are prescribed [26]. Tina Dietrich-Ntoukas (Berlin, Germany) stressed that the incidence of GVHD rises with age, and ocular GVHD is driven by inflammation, affecting the lacrimal gland, subsequently leading to atrophy and loss of tear film production. This leads to conjunctivitis, fibrosis of eyelids, keratitis and defects of the cornea. Guidelines have been published in Germany for ocular GVHD and proposals for a new grading scale for GVHD were developed [27]. Robust evidence for the use of SED is not high, with mainly anecdotal experience of good reported clinical outcomes. In GVHD patients who need cataract surgery, the use of SED prior to surgery has been recommended [28].

Philipp Roberts (Vienna, Austria) reported on neurotrophic keratopathy, which is characterized by damage of the trigeminal nerve down to the corneal sensory nerves [29]. Decreased corneal sensitivity leads to decreased blink rates, reduced tear production and subsequently epithelial breakdown with lesions and secondary ulceration. Neurotrophic keratopathy has three clinical stages: minor punctuated lesions on the surface of the cornea, followed by ulceration and finally perforation of the cornea. In stage 1, the use of artificial tears is recommended, preservatives should be avoided and at least in stage 2, SED are indicated [30]. Treatment is conservative and focuses on the avoidance of corneal transplantation.

Saaha Rauz (Birmingham, Great Britain) described a UK registry for OSD and a diagnostic classification that has allowed the use of autologous and allogeneic SED for patients [31]. Of interest was the use of allogeneic SED for frail patients or those who are not fit for apheresis. Allogeneic SED are classified as an unlicensed hospital special medicinal product in the United Kingdom. Data from the registry and outcomes were reviewed using a Delphi process [32]. Eight groups of indications for patients who might benefit from SED were generated. Importantly, reimbursement by the UK National Health System (NHS) has enabled much easier and earlier usage of SED.

Although many OSD are amenable to treatment by EDHO, robust efficacy data and clear indications for use are still lacking. Systematic reviews do support the use of EDHO in these diseases [33, 34].

CURRENT PHARMACEUTICALS AND OUTCOMES

Christian Gabriel (Graz, Austria) described other pharmaceutical products for the treatment of DED and pharmacological requirements for eye drops. The European Pharmacopoeia stipulates a pH of 7.1–7.5, an isotonic level of 250–300 mosm/kg. Additional preservatives are common, especially in aqueous eye drops. Specific viscosity ensures the

even spread of the pharmaceutical substance but can contribute to blurring of vision. Application includes warming the eye drops to 34°C and pressing the lacrimal duct while keeping eyes shut for some minutes. Hyaluronic acids are a mainstay of pharmaceutical eye drops in DED as they increase the excretion of water and mucins on the ocular surface and consequentially contribute to better tear film stability. The superiority in comparison to aqueous eye drops or saline is evident [35].

Piera Versura (Bologna, Italy) indicated that currently a consensus is needed for the use of various blood-based treatments for severe DED and the criteria for selection in each individual patient [36]. Clinical experience shows that most EDHO are chosen too late in the algorithm of therapeutic options for patients. Moreover, in most studies done on DED, the inclusion criteria were too diverse and prevent direct comparisons between the studies [37]. In addition, subjective criteria like the Ocular Surface Disease Index (OSDI) score may not correlate with the quantitative measurements of damage to the corneal surface [38].

Take-home points:

1. Various OSD are amenable to treatment with EDHOs and systematic reviews support their use. Further well-designed randomized clinical trials and robust data would be useful to define their role in treatment guidelines.
2. Reimbursement in health systems has enabled improved access and usage of EDHO and promoted their use in earlier disease stages.

DONATION OF STARTING MATERIALS AND MANUFACTURING

Birgit Gathof (Cologne, Germany) described the increase in use of allogeneic SED due to the reduction in autologous SED use in Cologne due to patient's health issues or frailty. Blood for allogeneic SED is collected from male repeat donors with preselected blood groups. The blood group is matched to minimize the use of 'universal' donors with blood group AB. Allogeneic SED have, however, not reached the required level of evidence and efficiency to persuade insurers to finance this new product.

Christian Gabriel discussed the use of autologous donations for EDHO, which are the most common form of donation but require careful donor management: Many donors may not be eligible for autologous blood donation. Donor criteria in autologous SED are not well-established and donor eligibility is usually determined on an individual basis with considerations for medication, blood pressure, chronic infections and cardiac function.

Production of SED

Denese Marks described manufacturing SED in a large blood establishment. The process requires a number of steps, including donor screening, blood collection, blood processing and SED packaging. Product stability and storage are also important considerations. The

preparation of autologous SED begins with a review of prescriptions from a patient's ophthalmologist as well as fitness for a blood donation. Additionally, not all patients are able to give a full-volume donation, making it harder to standardize the production process.

Whole blood is collected in a dry pack without anticoagulant and sent to a regional blood processing centre where the serum is separated and diluted to 20% with 0.9% saline. The serum is then dispensed into the individual ready to use dispensing vials. A sample from each diluted batch is retained for bacterial contamination screening. The final product is frozen and distributed to the patients via their nearest hospital. Up to 12 month's supply can be provided, where it can be stored in a domestic freezer in the patient's home. Stability studies have confirmed that SED can be stored in vials up to 12 months [39].

Given the constraints associated with producing autologous SED and increasing demand for this product, allogeneic SED are more cost-effective; and allow for simplification of the manufacturing process. Transition from autologous to allogeneic SED requires further process standardization and development of specifications to guide manufacturing.

Dirk de Korte (Amsterdam, The Netherlands) represented another large European facility producing allogeneic EDHO. In the Netherlands, only a limited number of patients use autologous SED due to concurrent medical conditions and only a limited number of hospitals are capable of preparing SED. Allogeneic male donors are tested for the absence of infectious diseases markers as required for blood donation, and serum is quarantined for 4 months. Testing for herpes simplex virus 1 and 2, cytomegalovirus (CMV) and varicella zoster virus may be added after consultation with ophthalmologists. To avoid putative side effects of isoagglutinins, only blood group AB donations are used for SED and up to eight donations are pooled for more homogeneous composition. Sterile filtration and further processing in closed systems are performed to minimize the microbial contamination. Pools are separated into 240-mL aliquots and stored at $\leq -25^{\circ}\text{C}$. Retention samples from each batch are also frozen. Selected growth factors and cytokines are measured. Depending on the pack system, the serum may be used undiluted or diluted 1:1 with 0.9% saline, the drop volume may be about 7 μL or conventional 50 μL . Vials are labelled and packaged for transport as required. The shelf life is 2 years at $\leq -25^{\circ}\text{C}$ or 18 months at $\leq -25^{\circ}\text{C}$, with an additional 6 months at $\leq -18^{\circ}\text{C}$ in hospitals and at the patient's home. After thawing, the shelf life is 24 h at 4°C or 8 h at room temperature [40].

Embedded into this process is the automation of production presented by Eddy Hilbrink (Mu Drop, Apeldoorn, The Netherlands). A production system was presented, which enables application of SED in very small volumes of 7 μL . This reportedly minimizes the systemic side effects, such as reflex tear production, wash-out and subsequent over-usage. This reduces serum use due to reduced wastage, lower product thawing time and avoidance of sticky eyelids.

In comparison to big institutions, Gerda Leitner (Vienna, Austria) showed her concept of a small-scale workflow for autologous SED, modified from a published protocol [41]. In brief, 230 mL of whole blood is collected from the patients. After coagulation at room

temperature and centrifugation, the serum is collected and diluted to 20% with balanced salt solution prepared in a sterile environment (Meise). After sterile filtration, aliquots are stored at 4°C for quarantine until the sterility is confirmed. It takes 4 weeks from the production to the release of autologous SED. In the allogeneic setting, a volume of 350 mL of whole blood is drawn from donors. Allogeneic blood group AB SED are produced in a closed bag system to provide an inventory for emergencies. The SED are tested for sterility, and active substances are stable at –20°C for 6 months [42].

Pathogen reduction (PR) may be needed for allogeneic SED production. Thierry Burnouf indicated that bacterial safety can be provided by implementing good manufacturing practices and sterile filtration and can be controlled by bacterial sterility testing of the final batch of EDHO [43]. Viral safety, in contrast, cannot be ascertained by final product testing and is, therefore, a concern of relevance for the safety and quality, especially of pooled allogeneic EDHO. The viral safety of allogeneic EDHO relies on the safety nets already in place at blood establishments to produce blood components for transfusion. Such safety nets encompass epidemiological control of the donor population, screening of blood donors for transfusion-transmitted diseases, testing of donations by serological and/or nucleic acid testing for relevant blood-borne viruses, and traceability. Platelet concentrates as potential starting material to produce EDHO may undergo PR with licensed amotosalen/UVA or vitamin B2/UVB illumination [44, 45]. Possible impacts of these PR procedures on EDHO safety and function are still lacking. PR procedures used for clinical plasma products and for human platelet lysate (hPL) used for clinical cell manufacturing are not licensed for EDHO. Technologies for the potential PR of EDHO exist and may theoretically be implemented, considering their respective efficacy against viruses affecting the eyes, allogeneic donor-associated risk factors and lack of toxicity for ocular administration.

Mickey Koh (London, Great Britain/Singapore) stressed the importance of consistent and harmonized labelling of EDHO by the use of ISBT128, the worldwide standard for coding of medical products of human origin (MPHO), coordinated and managed by the International Council for Commonality in Blood Banking Automation (ICCBBA). Its product code terminology enables a more accurate definition of EDHO and provides the ability to precisely define its various attributes, which will include different parameters like pooling, processing steps, source, donor classification and storage conditions. Importantly, the use of ISBT128 labelling would underline the need for EDHO to comply with the guidance and regulatory frameworks that apply to all MPHO [46].

QUALITY CONTROL

Dirk de Korte presented an approach for the quality control of SED. CMV is the most prominent virus found in serum, leading to discard in less than 1% of donations. Release of aliquoted sera is based on bio-burden measurement, filter integrity and endotoxin testing. Every batch is tested for functionality of the containers, especially the re-

closure of vials. Storage at temperatures less than –25°C has little effect on growth factors [47]. Extensive *in vitro* studies using keratinocyte cultures and human umbilical vein endothelial cell cultures have demonstrated proliferation in response to serum that had been frozen for 6 months. Scratch assays indicated good wound healing of serum stored over 2 years. Serum stored for 6 months at 4°C showed a significant decrease in growth factors, but the cell culture responses were only minimally reduced [48].

Katharina Schallmoser (Salzburg, Austria), presented established standards for hPL in the use as ancillary materials [49]. Microbiological control (sterility, endotoxins and mycoplasma) and analyses of haemoglobin, osmolality, total protein and cellular impurities are performed as required by the European Pharmacopoeia 9.0 (chapter 5.2.12). For platelet concentrates and hPL used as EDHO, currently there are only few guidelines available. In 2013, the Italian Society for Transfusion Medicine published recommendations for blood components for non-transfusional use [50]. They recommended the preparation in transfusion centres by using specific medical devices, ensuring sterility, identity and traceability, resuspension in plasma and maximum storage duration for 24 months below –25°C. Further guidelines for ‘Blood components for topical use or injection’ are available in chapter 35 of the European Directorate for the Quality of Medicines (EDQM). Due to lack of standardized production protocols, there is a huge variability in platelet-derived products with different compositions and efficacies. Therefore, EDQM guidelines recommend at least the evaluation of platelet recovery and essential growth factor concentration as quality control. In addition, for allogeneic products, biochemical analyses (pH, total protein, albumin, lipids, glucose and ferritin), isoagglutinin titration and performance testing in reference cells may be considered.

Take-home points:

1. Autologous EDHO have the most data, can be produced in the outpatient setting and require no matching. However, its variability, exclusion criteria and certain pathologies hampering autologous collection may mean a substantial benefit for the use of allogeneic EDHO, ensuring a more consistent and standardized process and a more traditional ‘pharmaceutical’ product.
2. PR strategies are of particular interest for allogeneic EDHO production depending on the number of donations pooled. Potential PR technologies for EDHO exist and could be evaluated considering their respective efficacy against viruses affecting the eyes. However, these are currently not licensed for EDHO.
3. Consistency with the use of ISBT128 labelling allows for a more accurate definition of EDHO and provides the ability to precisely define its various attributes. Labelling is also central for traceability of EDHO, an essential component of all MPHO.
4. Robust quality control and standards in the production of EDHO are needed. A similar strategy like that used for the production of hPL could be adopted for EDHO. Such quality controls need to be extended into each step of production including length of storage and functionality of the vials or containers.

NEW DEVELOPMENTS

Amniotic membrane extract eye drops (AMEEDs) are a promising new treatment for OSD. Most of the beneficial effects of AMEED are attributed to growth factors such as fibronectin, EGF and basic fibroblast growth factor, which are potent sources for corneal regeneration [51]. Following collection, the AM is frozen in liquid nitrogen, pulverized, aliquoted into vials and lyophilised, facilitating storage at room temperature. The product is reconstituted in sterile water and has a shelf life of 15 days. The results of phase I and II clinical trials were reported by Rita Piteira (Barcelona, Spain). In both trials, treatment with AMEED led to improvement in ocular surface symptoms, such as ocular pain, hyperaemia, eye stinging and burning [52, 53]. A phase III trial is now underway. The cost of preparing AMEED may be less expensive than the current SED.

Paolo Rebullà (Milano, Italy) described eye drops that can be produced from CB and cord blood platelet lysate (CB-PL). Preparation of CB-PL eye drops involves collection of the cord, removal of the CB and manufacturing platelet lysates. As with SED, the lysate is frozen in applicator vials and can be thawed by the patient as required. This process is more complex than collection for SED. However, platelet lysate is rich in a variety of growth factors and has demonstrated efficacy in many wound healing applications [54]. In a clinical evaluation of CB-PL eye drops, 33 patients with corneal lesions received eye drops four to six times per day for 19 days. Of these, 78% showed full or partial recovery and healing of ulcers following treatment, supporting further development and clinical studies [55]. The number of CB transplants is decreasing worldwide, and this product could utilize otherwise discarded biological starting material [56].

Marina Buzzi (Bologna, Italy) also found that CB is a ready-made source, as more than 80% of the CB units collected are not suitable for transplantation. The levels of many growth factors are higher in CB-serum (compared to peripheral blood serum) [57]. In a first study of 30 patients with corneal damage, all subjective parameters were significantly improved after using CB eye drops for 14 days. A second randomized clinical trial was designed to compare allogeneic SED to CB-derived eye drops. A reduction of corneal damage was observed in both arms and there was an improvement in the CB arm (higher OSDI score and secondary endpoints), possibly due to the higher growth factor content of CB [58].

The primary objective of the AmuSED trial (Dirk de Korte) was to determine whether allogeneic micro-sized SED (muDrop applicator) were non-inferior to conventional sized SED (Meise applicator) in patients with severe DED [59]. Overall, the study demonstrated that serum muDrops are non-inferior in terms of OSDI score and tear break-up time.

Neera Jagirdar (Atlanta, GA, USA) indicated that the disadvantages of autologous SED led to the development of a proprietary fibrinogen-depleted platelet lysate. This product was used in 10% and 30% solution in a prospective, randomized controlled double-blind study for the treatment of ocular GVHD. The products were compared to a control substance for 7 weeks in 64 patients. The new platelet lysate product was safe and well-tolerated with an

improvement in patient-reported parameters although larger studies are needed to confirm these effects [60].

Friedrich Paulsen performed the experiments with gold particles for the enhancement of secretion of growth factors and cytokines in the serum [61]. Gold particles have anti-inflammatory effects and promote cytokines and growth factors thereby serum treated with gold particles are improving regeneration [62].

Take-home points:

1. There is promise in novel EDHO compared to traditional SEDs with small clinical trials demonstrating efficacy.
2. Such novel EDHO includes using starting materials with a different cocktail of growth factors and substances present compared to serum.
3. Novel EDHO have explored the advantages of allogeneic over autologous production.
4. Micro-sized eye drops have been found to be non-inferior to conventional sized drops.

REGULATION OF EDHO

Verena Plattner (Vienna, Austria) highlighted the variation of regulations in Europe. Three countries regulate EDHO as advanced therapeutical medicinal products (ATMPs), two as non-ATMP medicinal products, seven as blood products and eight without any regulation. In a statement by the European Commission, there is the notion that EDHO may fall under the blood directive. But currently member states are responsible for the classification of EDHO. In Austria, blood donation for SED is regulated by the Austrian blood law; production and distribution are regulated similar to pharmaceuticals. This cumbersome process to gain any licence hampers the manufacture of EDHO for blood centres. To circumvent this, all SED in Austria can be produced as magistral formulations by prescription of a physician and may be issued to the patient by a pharmacy.

Johannes Blümel (Paul Ehrlich Institute [PEI], Langen, Germany) explained that blood is exempt from pharmaceutical regulation, but in Germany, SEDs are classified as pharmaceuticals. Regional authorities grant manufacturing licences under the guidance of PEI. It focuses on infectious disease testing as in the eye, the infectious dose may differ from that of blood transfusion; and neurotrophic viruses might be of relevance. For example, CMV can replicate on corneal epithelia, but flavi- and adenoviruses should also be considered. As such, viral inactivation should be considered, especially in pooled products. Two “orthogonal” viral inactivation steps are preferred in larger pools reduce risks from enveloped and non-enveloped viruses. The risk for transmissible spongiform encephalopathy should also be considered, so younger donors should be selected to minimize this risk.

Simonella Pupella (Rome, Italy) introduced the different regulatory approach in Italy. The European Blood Directive 2004/33/EC allows the member states to regulate new blood products such that national competent authorities should notify the European Commission with a view on Community action. In 2015, this enabled Italy to

regulate EDHO under the blood regulations, and collection, testing and production of EDHO are only allowed in blood establishments. Only autologous products may be collected and processed under supervision of the blood establishment, and the starting material may not exceed 60 mL.

Take-home point:

1. EDHO regulation varies among jurisdictions, including classification as a blood product, a pharmaceutical or an ATMP. Harmonization in this area is needed as it can also fall under both blood and medicinal product guidance.

CONCLUSION

1. The beneficial effects of EDHO are well-documented, but the effectors of EDHO are not fully known. Effects may be dependent on the content of lipids, growth factors, anti-inflammatory factors as well as pH, viscosity and osmolality.
2. A minimum set of quality parameters for SED is yet to be established. Also, the production process is not standardized.
3. Packaging and application issues of SED may reduce wastage and costs by leveraging clinical effectiveness.
4. Allogeneic SED are preferred due to higher manufacturing consistency, lower costs, ease of collection and use, especially in patients unsuitable for blood donation.
5. EDHO is being used in OSD and currently, is more often used in later treatment pathways of OSD when frontline therapies have failed. Robust efficacy data and clear indications for use are still needed and more studies should be undertaken to confirm its place role in treatment algorithms including frontline use.
6. Lack of reimbursement for EDHO is a major obstacle to earlier or broader use for treatment of OSD.
7. Variability in autologous SED usage, production and clinical criteria have hampered direct comparison of outcomes in clinical studies.
8. Regulations for EDHO are heterogeneous. The majority of European countries selected national blood regulations in this field. EDHO are part of MPHOS and the essential requirements for all MPHOS should apply.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

ORCID

Christian Gabriel  <https://orcid.org/0000-0003-2043-9320>

Denese C. Marks  <https://orcid.org/0000-0002-3674-6934>

Reinhard Henschler  <https://orcid.org/0000-0002-5895-4259>

Katharina Schallmoser  <https://orcid.org/0000-0002-7204-0058>

Thierry Burnouf  <https://orcid.org/0000-0002-0507-9243>

Mickey B. C. Koh  <https://orcid.org/0000-0002-4368-2502>

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