European Review for Medical and Pharmacological Sciences 2020; 24: 8642-8652

Dry eye disease treatment: the role of tear substitutes, their future, and an updated classification

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Abstract. – OBJECTIVE: The aim of this review is to summarize the results of a consensus meeting held by a group of experts in dry eye disease (DED) to discuss the importance of tear substitutes in the treatment of DED. The meeting focused especially on the main characteristics of lacrimal substitutes, the development of *in vitro* models to investigate DED pathophysiology and treatment, the importance of conducting rigorous clinical trials, the requirements of the upcoming European Legislation on medical devices, the advances in the formulation of safer preservatives, the peculiarities of treatment in younger subjects, and the importance of an updated terminology for lacrimal substitutes.

MATERIALS AND METHODS: A literature search was conducted using MEDLINE, with different combinations of pertinent keywords, depending on the subject under discussion, such as "dry eye disease"; "tear substitutes"; "*in vitro* models"; "ocular surface"; "clinical trials"; "European Regulation"; "preservatives" "younger patients". Also, each author included in the discussion selected articles from their personal library. Using a consensus-based method called nominal group technique to reach a conclusion and proposal for a new classification of eye drops used to improve the tear film and ocular surface epithelia, the experts also conducted a round table meeting.

RESULTS: The new terms proposed by the authors are "wetting agents", "multiple-action tear substitutes" or "ocular surface modulators". The new classification is needed to distinguish eye drops used to improve the tear film and ocular surface epithelia, in line with the new definition of DED, which recognizes the loss of ocular homeostasis, and the creation of a vicious circle of chronic inflammation and ocular damage as fundamental aspects of DED pathophysiology.

CONCLUSIONS: Although tear substitutes have been historically used to provide eye lubrication to the ocular surface, recent advances in the pathophysiology of dry eye disease (DED) clarified that treatment should not just focus on tear film quality or quantity, but address the loss of homeostasis of the ocular surface, blocking the vicious circle of chronic inflammation and ocular damage. Given the scant comparative evidence on tear substitutes currently on the market, further studies should focus on developing new agents, considering the advantages provided by *in vitro* models, importance of conducting rigorous clinical trials, availability of less harmful preservatives and obligations related to the new European legislation on medical devices. Based on the discussion of these topics, a group of experts held a consensus meeting to identify new and more appropriate terms for different tear substitutes. The proposed terms are wetting agents, multiple-action tear substitutes and ocular surface modulators. Regardless of the agent used, it is important to note that tear substitutes represent one of many options for

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DED treatment, which should not overlook the psychological aspects of the disease and the peculiarities of younger subjects, who seem to have a higher risk for DED, possibly related to digital devices excessive use.

Key Words:
Dry eye disease, Tear substitutes, Ocular surface, Consensus meeting, Wetting agents, Multiple-action tear substitutes, Ocular surface modulators.

Abbreviations

DED: Dry Eye Disease; OTC: Over-The-Counter; ESASO: European School for Advanced Studies in Ophthalmology; NGT: Nominal Group Technique; HCE: Human reconstructed *in vitro* Corneal Epithelium; IL-1β: Interleukin-1 beta; TFOS DEWS: Tear Film & Ocular Surface Society Dry Eye Workshop; EU: European Union; BAK: BenzAlkonium Chloride.

Introduction

Dry eye disease (DED) is a common disease encountered in clinical practice that has an increasing global health impact and important socio-economic consequences[1].

The assessment of the real epidemiology of DED has been challenging due to the lack of a standard definition of the disease. Multiple epidemiological studies have been conducted using different diagnostic criteria and thus reporting variable results, with a prevalence ranging from 5% to 50% in patients with and without symptoms, and up to 75% in some populations[1]. The disease is more prevalent among women and older people; however, recent reports suggest a considerable increase in DED symptoms in younger subjects than previously described, which has been linked to the widespread use of digital devices[2]. Indeed, the use of computer and other visual displays seems to have an important influence on DED symptoms, which have been reported in 30-65% of office workers[3,4], in 21% of boys and 24% of girls from high school[5]. Moreover, refractive treatment, including wearing contact lens and refractive laser, and cataract surgery are recognized as possible causes of DED symptom development[6].

The characteristic symptoms of DED are ocular discomfort and visual disturbances, and it may include foreign body sensation, ocular burning, dryness, redness, intolerance to contact lens, excessive tearing, photophobia, difficulty in opening the eye, itching, blurred vision, ocular fatigue and pain[7]. The symptoms have a major impact on the physical and psychosomatic well-being of patients, with an important negative influence on quality of life and a higher percentage of cases of depression, anxiety, stress, sleep and mood disturbances in DED subjects[8]. Ocular discomfort, pain and altered visual acuity may influence a patient's ability to perform daily activities, such as reading, watching television, driving and working, leading to important social constraints and economic burden[1].

The economic burden of DED is attributed to direct healthcare costs (medications and visits to a physician), its impact on the patient's quality of life and reduced work productivity. It is estimated that the annual cost of DED management equals to $3.84 billion in the USA[9], whereas in Europe, the annual total cost for 1,000 patients with DED managed by ophthalmologists ranges from $0.27 million in France to $1.10 million in the UK[10]. Moreover, DED causes decreased work productivity, not only for the time spent on treatment, but also the avoidance of certain workplace environments that may aggravate its symptoms. This results in an estimated annual productivity loss of $6,160 per patient in Japan[11] and an annual cost of $11,302 in the US[9].

The ultimate goal of DED treatment is the restoration of tear film homeostasis by breaking the vicious cycle that stimulates the disease[12]. Indeed, loss of tear film homeostasis is acknowledged as a critical point in DED pathogenesis, and as the source of a vicious cycle between tear film hyperosmolarity and ocular surface inflammation, which ultimately promotes the disease[13,14].

The historical mainstay of DED therapy consists of tear replacement with tear substitutes (also termed artificial tears), which are available mainly as over-the-counter (OTC) products in numerous topical formulations, such as drops, gels, ointments, or lubricants. The use of tear substitutes has been established to supplement insufficient tearing in patients and to provide the necessary eye lubrication needed to avoid eye complications; this should in turn help reduce tear evaporation and stabilize the tear film[15,16].

To address it appropriately, DED treatment should also aim to identify the major cause of DED in each patient (i.e., aqueous or evaporative causes). Although staged management and treatment recommendations should be followed, therapies need to be based on individual profiles,

characteristics and responses and should be not overly complicated for the patient. Therefore, a clear terminology is essential for defining the mechanism of action and efficacy of results obtained with each treatment, with a positive impact on DED overall costs as well.

Given the importance of tear substitutes for treating DED, a group of experts held a consensus meeting at the European School for Advanced Studies in Ophthalmology (ESASO; Switzerland) to discuss the main characteristics of lacrimal substitutes, the latest changes in the European legislation that impact medical devices, and the need of treating young patients with DED. Moreover, the experts discussed if the terminology used around tear substitutes is appropriate or whether it should be improved. The nominal group technique (NGT)[17] was used to determine a new classification that could replace the term "tear substitutes".

The Rationale and History of Tear Substitutes

Tear substitutes are electrolyte solutions consisting of different buffers and with widely different properties in terms of composition, presence and type of preservatives, duration of action, viscosity, osmolarity/osmolality and pH[18]. Each of these properties may influence the overall effects, use and tolerability of the tear substitutes for DED patients, eventually influencing their ability to protect and restore the ocular surface.

Scant literature exists on the impact of hyperosmolar or hyperosmolar tear substitutes on tear osmolarity and possible improvements in DED. The experiments conducted by Gilbard et al[19] on a DED rabbit model proved that hyperosmolar tear substitutes could reverse various damages to the ocular surface. These results were supported by two human studies, where the application of a hypotonic hyaluronic acid-based tear substitute led to an improvement in various signs and symptoms of DED[20,21]. However, more studies are needed to determine if the ability of lubricants to reduce tear film osmolarity has an impact on DED symptoms and signs.

Another important element is the retention on the ocular surface, which can vary depending on the lubricant formulation. Tear substitutes, which mainly have an aqueous base, include a variety of viscosity-enhancing agents that increase lubrication and prolong retention time on the ocular surface. The advantage of an increased retention time provided by high-viscosity drops is, however, balanced out by some inconveniences, such as transient visual disturbances and unwanted debris on the eyelids and eyelashes, which may negatively influence patient's tolerance and compliance towards treatment[22]. For these reasons, high-viscosity eye drops are typically recommended for overnight use, whereas low-viscosity eye drops are preferred for daytime[22]. Gels and ointments represent alternative treatments during the night and tend to be more viscous than tear substitutes and therefore provide the advantage of longer retention time. Retention time is an important element to consider when choosing the most appropriate treatment strategy for each patient, taking into account the severity of DED and the environmental changes to which eyes are subjected during the day and the night. One possible option is to combine different formulations to support the 24-hour variation in tear film characteristics[23].

As suggested by their name, tear substitutes attempt to replace and/or supplement the aqueous part of the lacrimal film; however, they do not target the underlying pathophysiology of the disease, and no data support their role in interacting with the ocular epithelium or influencing ocular inflammation[24]. However, some of the viscosity agents added to enhance lubrication and prolong retention time have some beneficial effects on the ocular surface beyond mere lubrication. Interesting results have been reported for hyaluronic acid, a glycosaminoglycan widely distributed throughout connective, epithelial, and neural tissues, which has been demonstrated to bind to the ocular surface, displaying potential wound-healing properties. In particular, hyaluronic acid seems to have beneficial effects by binding to CD44 and promoting the migration of human corneal epithelial cells *in vitro*[25]. It also improves the stabilization of the ocular epithelial barrier, thus preserving the corneal impermeability and the presence of an electric potential difference (i.e., the negative charge of outer cornea surface), therefore representing an electric shield towards possible bacterial adhesion and cornea infections[26].

Another interesting viscosity-enhancing agent that has shown beneficial properties towards the ocular surface is hydroxypropyl-guar, a polymeric thickener that increases the thickness of the mucous layer, protecting the ocular surface[27].

Despite the numerous beneficial properties of viscosity enhancers, such as increasing tear retention and tear film thickness, protecting the ocular surface against external stressors and des-

iccation, maintaining physiological corneal thickness and improving goblet cell density, these agents may also present adverse effects The most common adverse effect reported by patients after instillation is blurred vision, with variable levels of "ocular discomfort" and foreign body sensation This adverse effect is particularly common in products with increased viscosity, which are used by patients who do not respond to less viscous applications, and which are commonly used as overnight treatment given the negative effect on visual acuity Conversely, altered vision is less frequently reported with less viscous tear substitutes[22].

Currently, a huge variety of tear substitutes are commercially available on the market as OCT products, with extremely variable chemical formulations and presentations. Unfortunately, the supporting scientific evidence for most of these products is scant with inconsistencies in study design and reporting of the trial design, or they even lack supporting scientific evidence from human clinical trials[16]. Conversely, tear substitutes should be thoroughly studied in a research and development process built both on *in vitro* models and on the results of clinical trials.

Tear Substitutes Development: In Vitro Models

Different animal models, such as surgical removal of the tear-producing glands, inhibition of blinking to induce ocular surface desiccation, or inhibition of tear secretion by pharmacologic means, have been created to favor research on DED[28,29]. Unfortunately, these models require intensive effort from the researcher's side and are difficult to maintain and to be reproduced in the long term. New *in vitro* models that mimic human DED have therefore been developed. Three-D reconstructed human corneal epithelium models have been developed in the early 1990s and validated as standalone alternative to animal testing for Eye Irritation classification (OECD 492) to respond to a regulatory requirement. Given their biological relevance and reproducibility, they have become a suitable test system for mechanism-based preclinical models that can be used to investigate the pathogenesis of the disease and the effects of tear substitutes.

In 2011, Meloni et al[30] developed an experimental model of DED using human reconstructed *in vitro* corneal epithelium (HCE) and adapting culture conditions to induce the relevant modifications at cellular and molecular level to mimic dry eye. The *in vitro* DED model was used to define a biomarker gene signature of DED, which is characterized by an increase in MUC4, MMP9, TNF-α and *hBD-2* (DEFB2) gene expression. Moreover, the model was satisfactorily used for preliminary assessment of the protective activity of artificial tears[30].

In 2017, Barabino et al[32,33] further validated the relevance of the HCE model inducing a severe osmotic stress causing inflammatory pathways activation and impairment in the epithelial corneal cells tight junction's integrity, thus mirroring the features of dry eye conditions. The model was used to assess the potential effects of a new molecule, T-LysYal, a supramolecular system containing lysine hyaluronate, thymine, and sodium chloride that forms longer chains than hyaluronic acid, and a 3D structure with nanotubes[31]. The study showed that after 24 hours of treatment, T-LysYal was superior to hyaluronic acid in improving the ultrastructural morphological organization of 3D corneal epithelium and in increasing the expression of integrin β1 (ITG-β1). The results suggest the possible use of a new class of agents termed ocular surface modulators for restoring corneal cells damaged by dry eye conditions[32].

The DED model was recently further improved by including the contribution of the immunocompetent cells better mimicking the inflammatory pathway of the dry eye thanks to a new HCE model (HCE-CMM) allowing the infiltration of THP-1 cells. The efficacy of T-LysYal was tested in this innovative preclinical model that closely mimics the immune activation of DED. The authors showed that the T-Lysyal molecule was able to partially control the immunological response of the ocular surface, by significantly decreasing the expression level of CD86, CD14 and TLR4[33].

Lu et al[34] proposed another interesting approach to a model of DED, creating an *in vitro* 3D co-culture model. The model, composed of rabbit conjunctival epithelium and lacrimal gland cell spheroids, resulted in an enhanced secretion and expression of tear secretory markers, which were significantly increased by the direct contact between the two cells types. The authors tested the model to mimic DED (by inducing inflammation through proinflammatory cytokine interleukin-1 beta [IL-1β]) and to evaluate the response to treatment (in this case, dexamethasone as a commonly used therapeutic agent). The results showed that the co-culture system provided a more physiologically relevant therapeutic response compared with monocultures, and although still at the be-

ginning of the developmental phase, this complex 3D model may be further developed as a model for DED and therapeutic evaluation[34].

Tear Substitutes Development: Clinical Trial

Although there are many commercially available OTC tear substitutes, not many comparative clinical trials have been conducted to assess the superior efficacy of one product over another[35]. A recent meta-analysis by Pucker et al[16] represents an effort in this direction: the authors evaluated the effectiveness and toxicity of OTC artificial tear applications for treating DED as compared with another class of OTC artificial tears, no treatment, or placebo. They identified 43 randomized controlled trials with extremely heterogeneous characteristics with respect to types of diagnostic criteria, interventions, comparisons and measurements taken. Despite the limitations stemming from inconsistencies in study design and trial results reporting, the authors showed that OTC artificial tears may be safe and effective for treating DED and that the majority of OTC artificial tears may have similar efficacies. Nevertheless, additional research is needed to draw robust conclusions on the effectiveness of individual OTC tear substitutes[16].

Some indications on how to proceed with future clinical trials on DED come from the Tear Film & Ocular Surface Society Dry Eye Workshop (TFOS DEWS) II Subcommittee on Clinical Trial Design[36]. According to the subcommittee, a prospective, randomized, double-masked, placebo- or vehicle-controlled parallel group trial is the most desirable trial design. Other acceptable designs are crossover clinical trials, provided they fulfill specific requirements, and environmental or controlled adverse environment trials. An important effort should be put towards including biomarkers and/or surrogate markers in future trials on DED, although it is acknowledged that identifying and validating reliable biomarkers remains a matter of investigation[36]. Finally, it is important to point out that "non-inferiority" studies can represent a problem, because after numerous studies they can present limitations related to statistical changes.

The New European Legislation on Medical Devices

In April 2017, a new European Union (EU) Regulation on Medical Devices (MDR)[37] was introduced to replace previous outdated directives and will come into full force in May 2021, one year later from the original deadline due to the COVID-19 pandemic. The aim of the new regulation is to ensure safety, innovation and competitiveness in the field of medical devices (MD) in line with the important advances in this technology in recent years[38]. The new regulation places higher importance on how the biological evaluation of MD will be conducted long before any clinical test is performed and puts continued focus on the biological safety planning and implementation process, as well as on materials characterization. Moreover, according to the regulation, MD manufacturers should define a systematic method for gathering, recording and analyzing data on the safety and performance of their devices after they have been put on the market[38].

As tear substitutes are classified as MD, these changes in the legislation also apply to the ocular field and DED treatment. In practice, before entering the market, a new tear substitute product should be accompanied by a full technical file with regards to scientific proof of its efficacy, and a clinical trial should be performed at least 1 year from the launch of the product. The same rules will apply to tear substitutes currently on the market, for which a new and more robust documentation will be requested.

Preservatives: Pros and Cons

Tear substitutes are available both as single disposable units and as multi-dose packages for multiple applications. Whereas single units do not contain preservatives, in most cases multi-packages require the addition of preservatives to increase shelf life, prevent microbial growth and avoid the need for refrigeration during use[39]. Despite the important role played by preservatives in multi-dose formulations, increasing concern has been mounting in the last decade on the association between chronic use of preservative-containing topical products and ocular surface diseases, such as glaucoma[40].

Indeed, chronic exposure to preservatives is now recognized to have toxic effects on the ocular surface, especially for benzalkonium chloride (BAK), one of the most frequently used preservatives for ocular formulations. Multiple *in vitro* and *in vivo* studies suggest that BAK may damage the ocular surface in various ways, stimulating corneal and conjunctival epithelial cell apoptosis, damaging corneal nerves, delaying corneal wound healing, altering tear film stability and causing the loss of goblet cells[41].

Alternatives to standard preservatives have been proposed to avoid or reduce the adverse side effects of these agents while maintaining the advantages related to the multi-package formulations. One option is the development of less aggressive (and less studied) preservatives, such as EDTA, clorbuthanol, polyhexamethylene biguanide and polyquaternium-1[42,43]. Another alternative is represented by the so called "soft preservatives", which work by degrading either to chloride ions and water (sodium chlorite) or oxygen and water (sodium perborate) upon instillation and which seem to be less harmful to the ocular surface compared to BAK. These oxidative preservatives include GenAqua™ (sodium perborate) Purite® or OcuPure™ (sodium chlorite) Polyquad® (polyquaternium-1) and SofZia™ (boric acid, propylene glycol, sorbitol, and zinc chloride)[44]. Unfortunately, not all of these "soft-preservatives" have been comprehensively studied, and while considerable data are available on the safety and tolerability of Polyquad® as an alternative option to BAK in ocular formulations[45], further studies are needed to confirm the toxicity profile of some of these "less-harmful" preservatives. Another interesting strategy is the creation of innovative dispensers with unidirectional valves that allow multi-dose bottles to be preservative-free[22].

Despite the possible harmful effects of preservatives on the ocular surface, it is important to remember that preservative-free preparations are at risk of microbial contamination and should be discarded within a few hours from opening. Moreover, cost evaluations are important when choosing between the best eye drop for each patient, considering that preservative-free eye drops are associated with higher costs. Although ideally all prescribed dry eye products should be supplied in unit dose or preservative-free multi-dose bottles, preservative-free alternatives should be recommended, especially to patients who require frequent instillation during the day, such as those with severe DED[22].

Dry Eye Treatment For Young PatientS

Although older people have a higher risk of developing DED, the symptoms of the disease have increasingly been reported among children and teenagers as well, possibly in relation to the prolonged use of digital devices, such as computers, smartphones and tablets, which is extremely common nowadays and is recently increased with e-learning due to the COVID-19 pandemic[46].

Literature data on this topic are still scant, but the available data show a negative effect of smartphones and digital devices on ocular functions, such as blinking rate, tear function, and accommodative/binocular function[47]. This may result in ocular symptoms, such as blurring, redness, visual disturbance, burning, inflammation, lacrimation, and dryness, which have been reported both in adolescents and children after prolonged use of these devices. Moreover, children and adolescents are frequently contact lens users, which can negatively impact tear secretion and the well-being of the ocular surface[47].

In addition, especially for younger subjects, some anatomical factors should be considered, such as Meibomian gland atrophy, a condition commonly reported in the aging population[48] that has been recently identified in much younger subjects[49]. Another important aspect of treating children and adolescents with DED is that the pathogenesis is less known than in adults, and diagnosis is often overlooked. Some of the youngest patients present concomitant autoimmune, endocrine and inflammatory disorders, and should therefore be approached with a multidisciplinary team effort. While in some cases early detection allows prompt and successful treatment to eliminate the underlying causes of the disease, for some children, this may represent a lifelong problem, to be continuously managed to prevent ulceration and scarring of the ocular surface[50].

Treating children and adolescents with DED also presents some specific challenges, first of all the fact that younger patients tend not to complain about ocular symptoms, and in case of children that they are unable to participate in assessing subjective symptoms. Therapeutics approaches should consider the long-term perspective of medications, the peculiar condition of patients that are in the developmental phase, the availability of safe, non-toxic and preservative-free medication, and the survival curve of innovative treatments. Last, treatment options should be of limited cost (given the long-term perspective) and should be easy to use and allow for a prolonged use without complication: together with careful guidance provided to the parents, this approach should help obtain the best compliance from the patient[50].

Currently, there are a limited number of commercially available tear substitutes. We suggest

that more attention should be dedicated to the problem of dry eye in young patients. An interesting aspect that should be further investigated in this particular population is whether the excessive use of tear substitutes may decrease natural tear production.

A Proposal For a New Terminology

As stated in the previous sections, tear substitutes are of great importance for treating DED, and much has changed in recent years in terms of new treatment development and better understanding of the pathophysiology of the disease. We are now aware that DED is not just an alteration of tear film quantity or quality, but a thorough change of the ocular surface homeostasis with loss of the global ability to adapt and a shift towards evolving into a vicious circle of chronic inflammation and damage, in line with the revised TFOS DEWSII definition for DED that states: "*Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles*"[51].

Therefore, an important clarification should be made regarding the use of different products for DED. Experts agree that the term "artificial tears" should not be used in this context, as it is inappropriate given that tear substitutes are not similar to natural tears. In fact, the tear film consists of lipid, aqueous and mucin layers, which cannot be completely reproduced by artificial tear preparations. Artificial tears usually do not contain specific anti-inflammatory proteins, such as lysozyme, lactoferrin, immunoglobulin A and lipid-binding proteins[52], and they cannot interact with the ocular surface epithelia.

During a round table meeting, the experts discussed the importance of terminology regarding DED and using a consensus-based method called nominal group technique (NGT), they tried to reach a conclusion and proposal for a new classification of eye drops used to improve the tear film and ocular surface epithelia.

The NGT is a consensus method used to obtain consensus in different areas[53]. It is especially well-suited for obtaining consensus in small groups, where extensive face-to-face discussion and exchange of ideas can take place. The NGT is a structured group interaction and allows participants to express their opinions and allows opinions to be considered by other participants.

The NGT was used to broadly define three types of what has been previously described as "tear substitutes". The NGT phase began with the open question of defining the factors useful to support a new classification. The process involved four subphases: i) generation of ideas (basic answers to each question): expressed by each participant in an individual manner ii) collection of ideas: participants communicated their ideas, one at a time, in succession – round-robin session – to build an initial list of ideas (on a flip chart), with no discussion; iii) discussion of ideas: participants were invited to comment on each of the ideas proposed; in this phase, the ideas were refined and grouped, and debate was moderated by a facilitator; iv) prioritization/ranking of ideas to define the relative importance of the ideas with guided discussion followed by formal voting.

At the end of the NGT, the experts proposed to change the term "tear substitute" with the following ones: "wetting agents", "multiple-action tear substitutes" or "ocular surface modulators" (Figure 1). Wetting agents are molecules that can lubricate the ocular surface and have a limited residence time; multiple-action tear substitutes are molecules or combination of molecules that can improve the quality and quantity of the tear film components with limited capabilities to interact with the ocular surface epithelia; finally the term "ocular surface modulator" refers to polymers with scientifically demonstrated capability to interact with and influence the ocular surface components with particular regard to epithelial cells, promoting homeostasis and cellular well-functioning, and eventually modulating the inflammatory process.

Treating Dry Eye is Not Solely a Matter of Tear Replacement

Tear substitutes are only one of the options in the treatment armamentarium against DED. As reported in the TFOS DEWS II Management and Therapy Report, DED treatment may also include moisture chamber spectacles, anti-inflammatory agents (topical cyclosporine A, corticosteroids, and omega-3 fatty acids), tetracyclines, plugs, secretagogues, serum, contact lenses, systemic immunosuppressive and surgical alternatives[22].

It is not the subject of this paper to review all treatment options for DED, but it is now clear that the increased severity of the disease means that there is a need for an anti-inflammatory

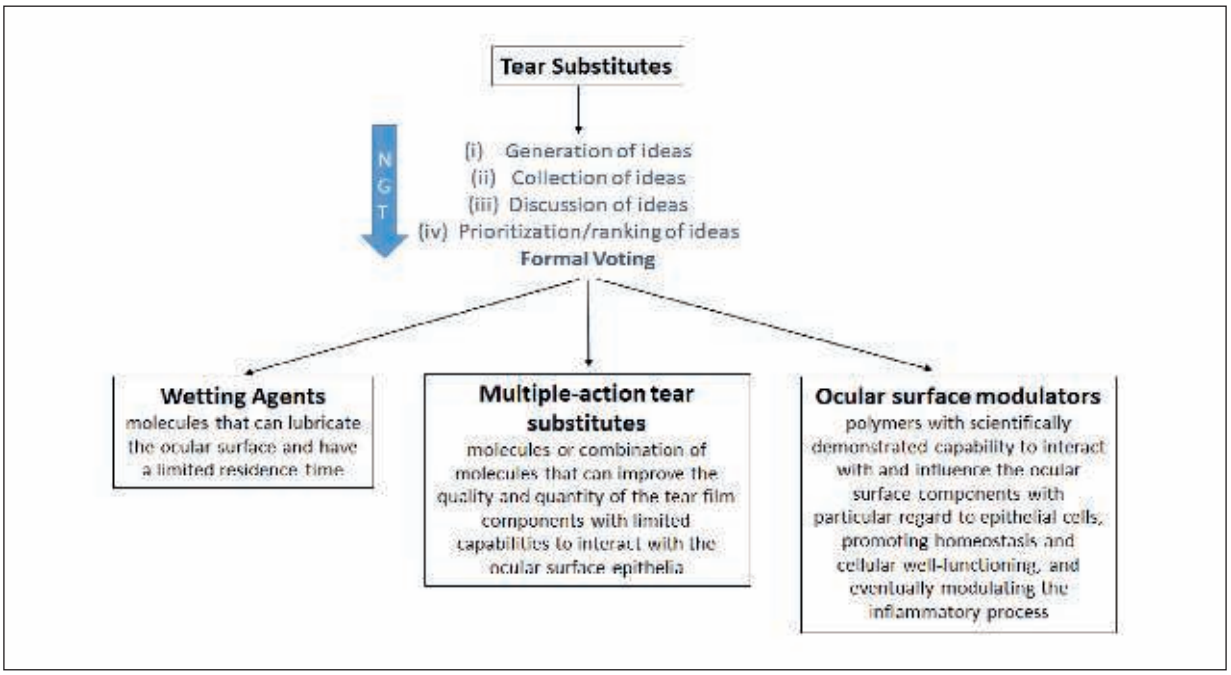

Figure 1. Main steps of the nominal group technique meeting and final proposed terminology for tear substitutes

treatment. The pathophysiology of chronic DED is characterized by inflammation that involves both the innate and adaptive immune responses. In chronic disease, both hyperosmolarity and inflammation are believed to be key pathological factors sustaining the condition by acting together on the ocular surface[54]. Therefore, independently from the source of the trigger, a self-sustained inflammatory response will develop on the ocular surface, eventually leading to persistent symptoms and signs. The three main options to control inflammation in DED are currently represented by cortical steroids[55], cyclosporine[56], and lifitegrast (currently available in the US only)[57]. However, it is important to note that these therapeutic approaches cannot be unique and fixed throughout the course of the disease, but should be for the long-term and be dynamic, adapting to the modifications on the ocular surface and be tailored on each patient's conditions[58]. An ideal therapeutic strategy should simultaneously address the following main targets: tear film quality and stability, epithelial morphofunctional changes, obvious and subclinical inflammation, and the structural and functional changes of nerves[58].

Finally, DED treatment should be accompanied by the management of the psychological aspects, which are crucial for the patients, given the higher percentage of depression, stress, sleep and mood disorders reported in patients with DED[7,8].

Conclusions

As emerged during the experts' meeting, many aspects of the use of tear substitutes for DED, starting from their very terminology, are still unclear and would need further clarification and standardization to help their use in clinical practice.

Developing new *in vitro* models, as well as exploiting the currently available ones more, will be essential in further exploring the pathophysiology of the disease and in understanding the basis for new tear substitutes' development and testing. Moreover, deeper investigation are needed through formal clinical trials to assess the differences in safety efficacy of the multiple tear substitutes currently available on the market, as well as to clarify the properties and safety of the newest "soft preservatives" (i.e., GenAqua™, Purite® or OcuPure™ and SofZia™), for which not much literature evidence is available.

Finally, future clinical studies should focus on the peculiarities of treating DED in younger subjects, given the increasing occurrence of this disease among younger patients.

Conflict of Interest

JMBdC: Alcon, Allergan, Bausch+Lomb, Santen, Thea. ML: Marc Labetoulle has served as occasional consultant for Alcon, Allergan, Bausch & Lomb, DMG, Dompé, Horus, MSD, Novartis, Santen, Shire, SIFI, Topivert, Thea. All the other authors declare no conflict of interest.

Acknowledgements

Editorial assistance was provided by Ambra Corti, Sara di Nunzio and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by Sildeha. The authors thank The European School for Advanced Studies in Ophthalmology (ESASO), Lugano, Switzerland for technical assistance during the meeting..

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Sildeha supported the editorial assistance of this manuscript.

Method of Literature Search

A literature search was conducted using MEDLINE, with different combinations of pertinent keywords, depending on the subject under discussion, such as "dry eye disease"; "tear substitutes"; "*in vitro* models"; "ocular surface"; "clinical trials"; "European Regulation"; "preservatives" "younger patients". Each author also included in the discussion selected articles from their personal library. Only English articles were included; no temporal limits were established.

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