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ORIGINAL RESEARCH

Real-World Treatment Outcomes of an Artificial Tear Containing Arabinogalactan, Hyaluronic Acid and Trehalose Among Subjects with Dry Eye

Andrea Bedei[1], Pedro Rocha Cabrera[2], Luis Oliveira[3], Laura Castellini[1], Giulia De Grazia[4], Stefano Remiddi[4]

[1]Ophthalmology Department Casa di Cura San Camillo, Forte dei Marmi, Italy; [2]Ophthalmology Department Hospital San Juan de Dios Tenerife, Santa Cruz de Tenerife, Spain; [3]Ophthalmology Department Hospital Santo Antonio, Porto, Portugal; [4]Department of Research and Development, MD Italy, Albano Laziale, Italy

Correspondence: Stefano Remiddi, MD Italy srl, Department of Research and Development, Via Cancelliera, 12, Albano Laziale, Rome, 00041, Italy, Email stefano.remiddi@md-italy.it

Purpose: To assess the efficacy, adherence, and tolerability of a new artificial tear based on arabinogalactan, hyaluronic acid, and trehalose in a population with dry eye disease (DED).

Methods: A retrospective, real-world, post-marketing study identified 96 adult patients (aged 18–80 years) with signs and symptoms of dry eye. These patients received fixed combination therapy with eye drops containing arabinogalactan, hyaluronic acid, and trehalose at various dosing schedules. The data for this study were collected from April 2022 to June 2023. Patients underwent evaluation at baseline (T0) and after a follow-up period of two–three months (T1) using a patient-reported questionnaire.

Results: In 96 adult patients (71 women and 25 men) with dry eye due to various conditions, the results indicated a 98% positive response to therapy. This response included improvements in vision (13%), comfort (39%), redness (13%), itching (16%), photophobia (4%), and tearing (14%). Additionally, 61% of the patients experienced 1–2 hours of comfort following instillation.

Conclusion: This real-life post-marketing study demonstrated clinical improvement of signs and symptoms in patients with dry eye disease using a new artificial tear medical device based on arabinogalactan, hyaluronic acid, and trehalose.

Keywords: dry eye, real-world study, arabinogalactan, hyaluronic acid, trehalose, post-marketing study

Introduction

Dry Eye Disease (DED) is a heterogeneous group of conditions characterized by disturbance of the lacrimal function unit secondary to reduced tear production or excessive tear evaporation associated with ocular discomfort. This can affect everyday activities.[1] The tear film plays an important role in maintaining high optical quality of the ocular surface by exerting trophic support on the corneal and conjunctival epithelial cells, thus providing the anterior part of the eye with refractive and antimicrobial functions.

The vicious circle of inflammation involving both innate and adaptive immune responses is now widely acknowledged at an early stage.[2]

Several studies have identified metalloproteinase-9 (MMP9) and lipopolysaccharide-induced secretion of leukotriene B4, along with other proinflammatory cytokines and chemokines, as inflammatory mediators in the pathogenesis of chronic dry eye disease. Moreover, increased expression and activation of enzymes leading to cellular and tissue damage has been demonstrated.[3]

These mediators, along with tear hyperosmolarity, have been demonstrated to induce the loss of goblet cells and damage the epithelial glycocalyx. Additionally, inflammatory mediators generated by activated T cells, which are recruited to the ocular surface, further exacerbate damage.[3]

DED tends to increase with age and its prevalence is higher in female than in male.[3]

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The Tear Film and Ocular Surface Society (TFOS) published the Dry Eye Workshop (DEWS) II Diagnostic Methodology report, which identified the most appropriate steps and techniques for performing diagnostic tests and monitoring DED, as well as guidelines for differential diagnosis.[4]

Arabinogalactan (AG) is a polysaccharide abundant in most plants, but it is usually obtained from the bark of larch trees (Larix occidentalis and Larix decidua) of the Larix species. It is composed of arabinose and galactose in a ratio of 1:6, with a small amount of glucuronic acid.[5,6]

Moreover, although AG has great morphological freedom, it typically exhibits a rigid triple spiral helical structure, whereas its lateral groups form flexible branches with numerous exposed hydroxyl groups. This characteristic behavior may confer mucoadhesive properties on the polymer, thereby playing a significant role in the treatment of dry eye disease (DED). AG interacts with corneal mucins, which play a pivotal role in maintaining tear film stability and quality.[2]

Hyaluronic acid (HA) is a glycosaminoglycan composed of repeating units of d-glucuronic acid and N-acetyl-d-glucosamine, which is an anionic, non-sulfated polymer, and a substantial connective tissue component. HA has been extensively studied and used in artificial tear formulations because of its efficacy in dry eye treatment. This is due to its ability to increase corneal wettability and stability of the pre-corneal tear film without altering the conjunctival epithelium.[7,8]

Trehalose, a disaccharide, serves as a protective agent against various environmental stressors including drying, dehydration, cold, heat, and oxidation. Among these functions, its role in safeguarding against drying and dehydration has been extensively investigated in ophthalmic research for the treatment of dry eye disease (DED).[9,10]

This study aimed to evaluate the efficacy, adherence, and tolerability of an artificial drop formulation containing arabinogalactan, hyaluronic acid, and trehalose in subjects with signs and symptoms of DED, evaluated at baseline and after a follow-up period, using a patient-reported questionnaire.

Materials and Methods

Study Design and Data Sources

This real-world retrospective cohort analysis was conducted in Spain and Portugal, where the product was first available in the EU at the pharmacy level in June 2021. The questionnaire described in Figure 1 was submitted to each patient at the time of enrollment (T0) and after the follow-up period (T1). In both countries, the date of the first patient-in (FPI) was April 2022, and the date of the last patient-out (LPO) was June 2023. Data were collected according to the principles of safety, transparency, and confidentiality, in full compliance with EU Regulation 2016/679, protecting privacy. This program was conducted in compliance with the ethical principles of Good Clinical Practices, the Declaration of Helsinki and the European Union (EU), pre-market and Post Marketing Surveillance processes as defined by Medical Device Directives (MDD) since 1992 and recently updated by Medical Device Regulation (MDR); therefore, approval from an Institutional Review Board was not required. Informed consent was obtained from all participants. Each patient was assigned to one ophthalmologist involved in this study. The criteria were respected in Spain, while in Portugal a few ophthalmologists enrolled two patients each. The doctors orally provided the patients with information about the therapy, including its use, dosage, dispenser, and all necessary details.

Patient Selection and Outcomes

The study group consisted of 96 adult patients with mild-to-moderate dry eye, severe dry eye, contact lens-induced dry eye, VDT-associated dry eye, corneal ulcer, dry eye after cataract surgery, dry eye after refractive surgery, dry eye post corneal transplantation, post-traumatic dry eye, and foreign body sensation.

The prescribed dose at the time of enrollment ranged from one to two drops per day, with the possibility of higher doses depending on the patient's needs.

The duration of the treatment, supported by clinical evaluation, ranged from two to three months.

Patients were evaluated after 60/90 days (T1), after which they were re-evaluated using a questionnaire with the scope to assess treatment outcomes, duration of comfort sensation, understanding of instructions to use the product, ease of use of the dispenser, impact on patient's quality of life, and overall feedback about the product.

VISIT T0 – Enrollment

Progressive number:

A. Personal information

Sex: ◯ Male ◯ Female

Age range: 18 – 34 35 – 50 51 – 64 65 – 80

B. Diagnosis/condition
- ◯ Mild dry eye
- ◯ Severe dry eye
- ◯ Contact lens
- ◯ Prolonged use of videoterminal
- ◯ Corneal ulcer
- ◯ Post-cataract surgery
- ◯ Post-refractive surgery
- ◯ Post corneal transplant surgery
- ◯ Trauma/foreign body

C. Treatment prescribed
- ◯ 1-2 drops a day
- ◯ 3 drops a day
- ◯ 4-6 drops a day
- ◯ On a need basis

D. Duration
- ◯ 1 month
- ◯ 2 months
- ◯ 3 months
- ◯ > 3 months

VISIT T1 – 60-90 Days follow up

A. During this last period of follow up, the product has been used:
- ◯ Exactly as prescribed
- ◯ For other conditions such as (please specify)
  - ◯ Ocular burning
  - ◯ Red eyes
  - ◯ Heavy lid sensation
  - ◯ Blurred vision
  - ◯ Other:_____

B. In case of different administration scheme of the product, please report the real number of daily administration followed:
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ > 5

C. Response to the therapy:
- ◯ Positive (please specify how, more than one answer is possible)
  - ◯ Better vision
  - ◯ Greater comfort
  - ◯ Reduction of redness
  - ◯ Reduction of itching
  - ◯ Reduction of photophobia
  - ◯ Reduction of tearing

  In case of positive response indicate the duration of the comfort:
  - ◯ < 30 minutes
  - ◯ 30 – 59 minutes
  - ◯ 1 – 2 hours
  - ◯ > 2 hours
- ◯ Negative (please specify how, more than one answer is possible)
  - ◯ Blurred vision
  - ◯ Increased redness
  - ◯ Itching
  - ◯ Burning
  - ◯ Other: _____

  In case of negative response indicate the duration of the discomfort:
  - ◯ < 10 minutes
  - ◯ 11 – 29 minutes
  - ◯ 30 – 59 minutes
  - ◯ 1 -2 hours
  - ◯ > 2 hours

D. In case of negative response to the treatment, the patient suspended the therapy?
- ◯ Yes ◯ No

E. The leaflet of the product has been evaluated clear by the patient?
- ◯ Yes ◯ No
- ◯ If negative, please specify: _____

F. Did the patient find the vial manageable at instillation?
- ◯ A lot
- ◯ Quite good
- ◯ Normal
- ◯ Little
- ◯ Very little

G. Did the use of the product improved the quality of life of the patient ? How ?
- ◯ Yes (please specify, more than one answer is possible)
  - ◯ Better visual comfort
  - ◯ Better vision
  - ◯ Resolution of dry eye sensation
  - ◯ Better tolerability of contact lens
- ◯ No (no improvement)

H. On the basis of the feedback of this patient and your clinical evaluation as an Ophthalmologist, what is the judgment regarding this product ?
- ◯ Very good
- ◯ Good
- ◯ Medium
- ◯ Sufficient
- ◯ Poor

Figure 1 Treatment Questionnaire.

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Results

This study assessed 96 adult patients (25 men and 71 women) with dry eye, documented symptoms, and ocular surface inflammation. The patients' ages ranged from 18 to 80 years old. At baseline, therapy was prescribed based on the presence of dry eye symptoms corresponding to the clinical conditions described in Figure 2

Each patient had the opportunity to provide multiple answers, as shown in Figure 2, and the highest percentage of patients complained of symptoms of mild and severe dry eye after cataract surgery.

The prescribed dosing schedule is illustrated in Figure 3, where the majority of patients were treated with three drops per eye per day, while 40% received continuous treatment for more than 3 months.

No correlation has been found between the number of drops received as a function of the different concomitant clinical condition.

At the first follow-up visit (T1), 60 or 90 days after the initiation of therapy, most patients (89 patients, 93%) followed the prescribed therapy, using the product for dry eye. The remaining patients (7 patients, 7%) used eye drops for different indications, as reported in Figure 4: blurred vision, red eyes or ocular burning.

A positive response to therapy was recorded in 98% of patients, with only a 2% discontinuation rate and ocular itching. As Figure 5 shows the improved comfort of the patients.

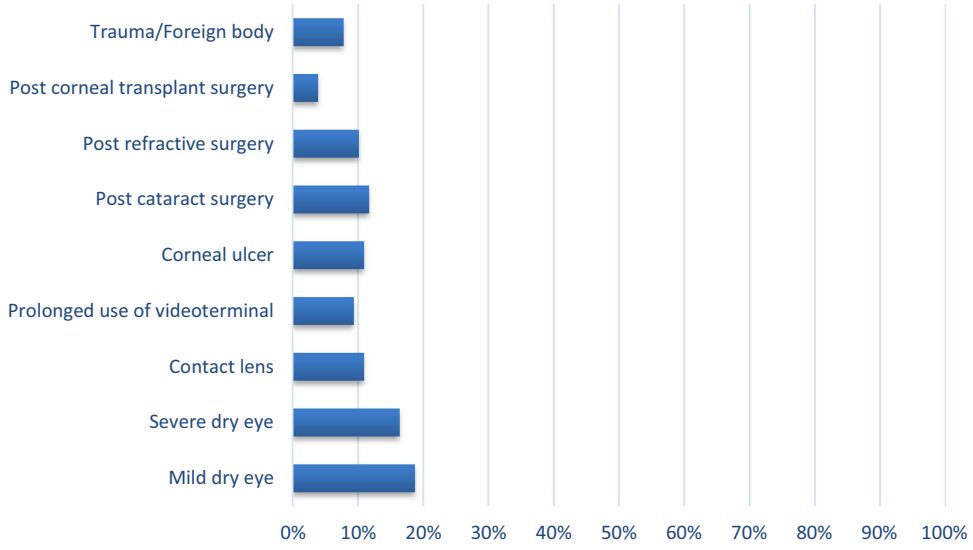

Figure 2 Clinical conditions at baseline.

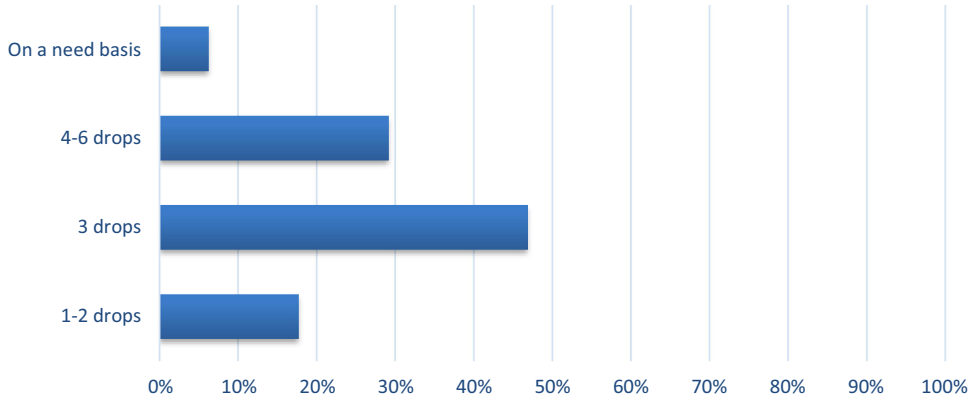

Figure 3 Prescribed dosing schedule.

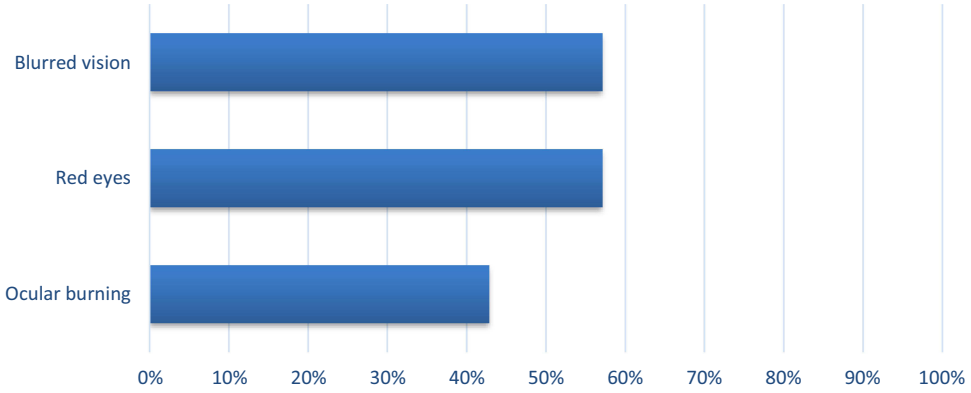

Figure 4 Utilization for other reasons.

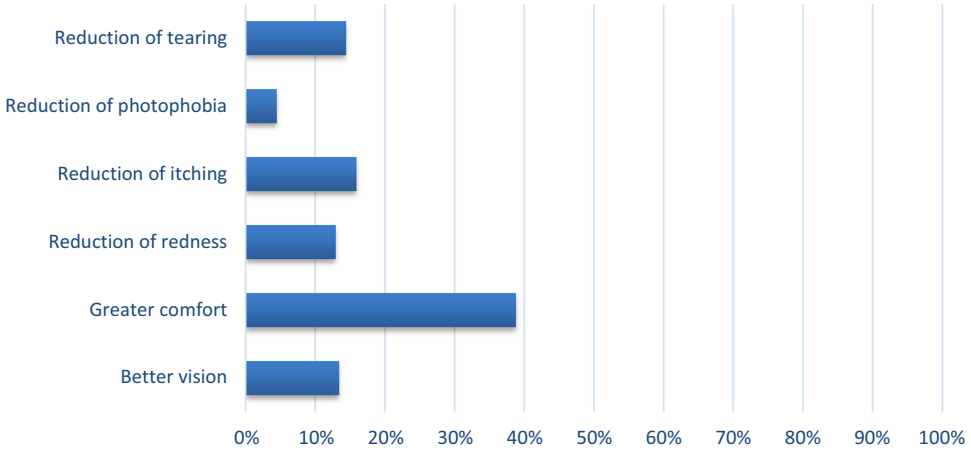

Figure 5 Positive response to the therapy.

Furthermore, instructions to use the product were evaluated clearly in 99% of the cases, and the dispenser was considered easy to use in 98% of the cases.

Finally, resolution of symptoms improved the patients' quality of life, as indicated in Figure 6.

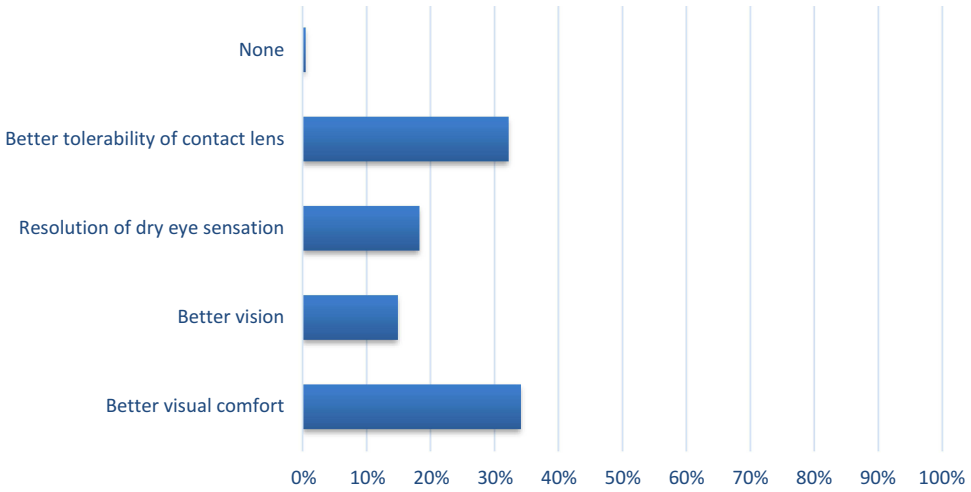

Figure 6 Improvement of the patient's quality of life.

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In summary, 96% of Spanish and Portuguese adult patients with dry eye and, in some cases, with multiple concomitant clinical conditions, expressed positive to very positive feedback after treatment, with an eye drop formulation containing arabinogalactan, hyaluronic acid, and trehalose.

Discussion

Dry eye disease (DED) is a common disorder in daily clinical practice and a growing challenge, with a significant negative impact on patients' quality of life and productivity. Several studies have shown that its prevalence increases with age and mainly affects women.[3,4]

This study included a group of patients treated with a new artificial tear medical device based on arabinogalactan, hyaluronic acid, and trehalose. In addition to efficacy and safety parameters, we conducted a real-life post-marketing study to evaluate the impact of dry eye on the daily life of patients. Ophthalmologists administered a questionnaire to all 96 patients at enrollment and after a 60/90 days follow-up period. Initial symptoms such as mild and moderate dry eye, contact lens discomfort, corneal ulcer, dry eye after cataract surgery, dry eye after refractive surgery, dry eye post corneal transplant, post-traumatic dry eye, and foreign body sensation were evaluated. This study was conducted in accordance with post-marketing EU regulations to evaluate the impact of a product after its market availability to track any possible adverse effects.

Medical devices are the backbone of modern health care systems. Given their importance in daily medical practice, manufacturing, marketing, and clinical processes should be regulated at all levels. Harmonized evidence-based conformity assessment of medical devices during post-market surveillance (PMS), relying on the traceability of medical device measurements, can contribute to increased reliability of medical device performance, and consequently, to higher reliability of diagnosis and treatment models.[11]

This study demonstrated improvements in the quality of life, with 96% providing positive feedback. These results are in line with those of our previous clinical study, in which improvements in clinical signs and symptoms of dry eye were demonstrated in 25 patients receiving eye drops containing arabinogalactan, hyaluronic acid and trehalose.[12]

The results showed, in the real-world use of this kind of products, a broad variety of concomitant clinical conditions, in addition to the basic dry eye symptoms, in this regard we found, for example, several conditions related with surgery and ER setting, as well the use of the product for other reasons where probably, there is an unmet need (blurred vision, red eyes and ocular burning).

The positive response to the therapy in this study was mainly driven by the sensation of greater comfort in general, rather than other more specific features; this was probably due to the lack of tear function tests not included in the study design and for the subjective, self-assessment evaluation of the patient. Nevertheless, the improvement of the patient's quality of life, was better described in terms of visual comfort and better tolerability of contact lens, for example.

The decision to use eye drops containing these three active components was based on the hypothesis of the relationship between inflammation and DED, and the patients demonstrated significant improvements in the reduction in the concentration of some inflammatory markers (such as MMP9) from baseline. Inflammation, including innate and adaptive immune responses, is a key element of the vicious cycle of DED. Mitogen-activated protein kinases and NF-kB signaling pathways, generation of inflammatory cytokines such as IL-1 and TNF-a and upregulation of matrix metalloproteinase (MMP) produced by epithelial cells are involved in acute response. The adaptive response is triggered by the activation and migration of resident antigen-presenting cells to the regional draining lymph nodes, where they stimulate naïve T cells (Th0), leading to the expansion of IL-17-G and IFN-G-secreting Th17 (Th17/1) cells.[13,14] Proteolytic enzymes, particularly MMP-9, play a key role in DED pathogenesis by disrupting epithelial cell tight junctions, resulting in breakdown of the ocular surface epithelial barrier. Recently, MMP-9 has been proposed as one of the best biomarkers of DED severity[15] and a diagnostic biomarker that can be assessed using point-of-care immunoassay.[16]

HA significantly improves tear film production in patients with ocular surface disorders. Several clinical studies have demonstrated the properties of HA by comparing the efficacy of HA- and non-HA-based eye drops for the treatment of dry eye disease, including saline and conventional artificial tears, for the treatment of dry eye disease.[17]

Trehalose is an osmoprotectant found in nature and is a disaccharide present in many non-mammalian species that allows cells to live in unfavorable environments. It is involved in anhydrobiosis and in the ability of some plants and

animals to tolerate prolonged periods of desiccation. It has a high water retention capacity and exerts the dual property of bioprotection and osmoprotection by preserving corneal epithelial cells from oxidative damage induced by UV rays, accelerating healing, decreasing conjunctival inflammatory cytokines, restoring the osmotic balance of the ocular surface, and preventing denaturation of cell membrane lipid bilayers and proteins to maintain the homeostasis of corneal cells. Trehalose protects corneal epithelial cells from desiccation and corneal and conjunctival epithelial cells against apoptosis. The first action is important because by preserving epithelial cells from dehydration, cell membranes are in a liquid crystal state, even when the water content is very low. Simultaneously, it protects epithelial cells from tear film hyperosmolarity by restoring the cell volume. A recent clinical study[18] demonstrated the efficacy of trehalose (at a concentration of 1.2%) in improving discomfort in patients with dry eye. In this study we compared trehalose 1.2% versus carboxymethylcellulose (CMC). Nine patients with DED were treated, in one eye with CMC twice daily in the contralateral eye for a period of thirty days. Inflammatory and autophagy markers were analyzed in vitro (corneas exposed to TNF-α and desiccation stress) and in vivo (BUT and Schirmer test values in the eyes of treated patients). The in vitro procedure confirmed that trehalose could reduce cellular and tear cytokine levels. The in vivo procedure showed that trehalose could reduce eye symptoms compared with CMC (contralateral treatment). These results are consistent with those reported in previous studies, demonstrating the in vivo efficacy of both components: high molecular weight HA 0.25% and trehalose 2%.

AG is a polysaccharide that is abundant in several plants, but it is usually obtained from the bark of larch trees (*Larix occidentalis, Larix decidua*). It is composed of arabinose and galactose in a 1:6 ratio, and a small amount of glucuronic acid.[5] The macromolecule, with a molecular weight ranging from 10.000 Da to 120.000 Da, has been approved by FDA for oral use, even in large quantities (FDA, 2000), for its biological properties and activities. These include protection of the gastrointestinal mucosa, improvement of vascular permeability, and enhancement of immune function.

AG solubilized in ophthalmic solution (from 0.2% to 10%) have been studied, showing Newtonian rheological behavior and viscosity values ranging from 1.00 to 1.58 mPa*s. Tear fluid has a viscosity of 1.02–1.93 mPa*s[11] and thickener agents are commonly added to ophthalmic formulations to prolong their retention time on the ocular surface.

AG (5% w/w) has been reported as a novel mucoadhesive polysaccharide that can be used to treat dry eyes and corneal wounds and to heal dry spots on the cornea. At this maximum concentration, the AG drops did not show any cytotoxic effects on the rabbit corneal epithelium, whereas 0.01% w/w benzalkonium chloride was highly toxic.[19,20]

After 24 h, the AG-treated cornea was well differentiated into an organized structure; after 48 h, they appeared normal, marked by the presence of microvilli and glycocalyx, an unorganized structure of cells of different sizes, lack of microvilli, and glycocalyx were found in the control formulation even after some days of administration.

In a recent in vitro study, AG in ophthalmic solution was compared to other artificial drops with and without preservatives on the amoebicidal effect responsible for *Acanthamoeba keratitis* (AK), a well-known severe ocular condition. AG demonstrated superior anti-Acanthamoeba activity, which induces programmed cell death in this protozoa, suggesting that AG-based ophthalmic products are a new source of anti-AK compounds.[21]

Other in vitro experiments have shown that the combination of AG and HA at a certain ratio can produce a synergistic effect and contribute to the reduction or inhibition of the enzymatic complex xanthine + xanthine oxidoreductase reaction (XOR), which normally catalyzes the formation of reactive oxygen species (ROS) and uric acid.[22–24] The synergistic effects of AG and HA were statistically significant. Uric acid inhibition due to the complex formed by the combination of AG and HA was statistically superior to the sum of the inhibitions of the individual components. The same behavior has been proven in the reduction of ROS; the combination of AG and HA entails a significant reduction in these toxic-free radicals, which is higher than the sum of the inhibition of the individual components. The in vitro synergistic effect of AG and HA has been a rationale for further clinical investigations on the beneficial effect of such eye drop formulations in mitigating the inflammatory process that leads to a worsening of dry eye disease.[25]

This synergistic effect was further confirmed by measuring the diffusion coefficient D of water protons by diffusion ordered spectroscopy technique (DOSY). Determination of viscosity and investigation of the affinity of a small-molecule molecular probe versus an AG/HA mixture in the presence of bovine submaxillary mucin (BSM) by[1] HNMR spectroscopy. Enhanced mucoadhesive properties, decreased water mobility, and decreased viscosity were observed with an increase in the AG:HA ratio and the total concentration of AG.[26] This recent experiment confirmed, by using different

techniques, the unique and virtuous interaction between AG and HA, which is supposed to form stable supramolecular aggregates that can incorporate more water molecules, resulting in less mobility and, ultimately, more persistent corneal hydration.

Limitations of this study include the lack of a control group and a complete statistical analysis of the results (initial vs treatment). Additionally, several patients were affected by concomitant disorders and no function test comparison was performed (eg vs BUT, Schirmer test) because the objective of the study was limited to the patient self-evaluation of the treatment in a real-world setting.

Conclusion

This is the first real-life post-marketing study that demonstrated clinical improvement of symptoms in a large sample of patients suffering from dry eye disease with the use of a new artificial tear medical device based on arabinogalactan, hyaluronic acid, and trehalose, evaluated after commercialization in two EU Countries. Patients who received this treatment for up to 2–3 months, also reported high adherence to treatment and a significant improvement in terms of quality of life.

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Disclosure

The authors declare no conflicts of interest that could have influenced the work reported in this paper.

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