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The New Era Approaches to Dry Eye Treatment

In a symposium sponsored by Santen held recently in conjunction with the 32nd Asia-Pacific Academy of Ophthalmology (APAO) Congress 2017 in Singapore, Professor Marc Labetoulle and Professor Wei Li shared their insights on the latest treatment options for dry eye disease.

Cyclosporine 0.1% Cationic Emulsion in The Treatment of Severe Keratitis with Dry Eye

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Three classes of treatments are currently available for dry eye disease (DED). Under tear substitutes, physiological saline, and derivatives of polyvinyl alcohol and methylcellulose are among the simplest. The second-generation tear substitutes include carbomers, hyaluronic acid, HP-Guar and the newest class, cationic emulsion, which is a mineral oil emulsion. Cyclosporine, a topical immunomodulator with anti-inflammatory properties, has also been added to the armamentarium of therapeutic options indicated for severe cases of DED that do not respond to the usual therapeutics.[1]

CYCLOSPORINE PREPARATIONS

The newest cyclosporine pre-paration, Ikervis® (cyclosporine 0.1% cationic emulsion), received market authorization in the European Union in March 2015. The market authorization was based on the results of the SANSIKA European phase III pivotal study that compared Ikervis® vs. its own vehicle.[2] The Ikervis® vehicle is the cationic emulsion, Cationorm®, which has an oily center, a surfactant that stabilizes the interface and a cationic agent that provides a positive charge (**Figure 1**).

MULTICENTER EUROPEAN STUDY DEMONSTRATES IKERVIS® EFFICACY AND TOLERABILITY

Conducted in nine European countries, SANSIKA is a multicenter, randomized, double-masked, 2-parallel-arm, 6-month phase III study with a 6-month open-label treatment safety follow-up. It evaluated the efficacy and tolerability of Ikervis® for the treatment of severe keratitis in 246 patients with DED. Patients with severe DED, defined as corneal fluorescein staining (CFS) grade 4 on the modified Oxford scale (**Figure 2**), Ocular Surface Disease Index (OSDI) of at least 23, and Schirmer test between 2 and 10 mm/5 minutes were randomized to receive Ikervis® or its vehicle once-daily.

FIGURE 1. Cationic nanosized droplets transport ciclosporin to the corneal cells

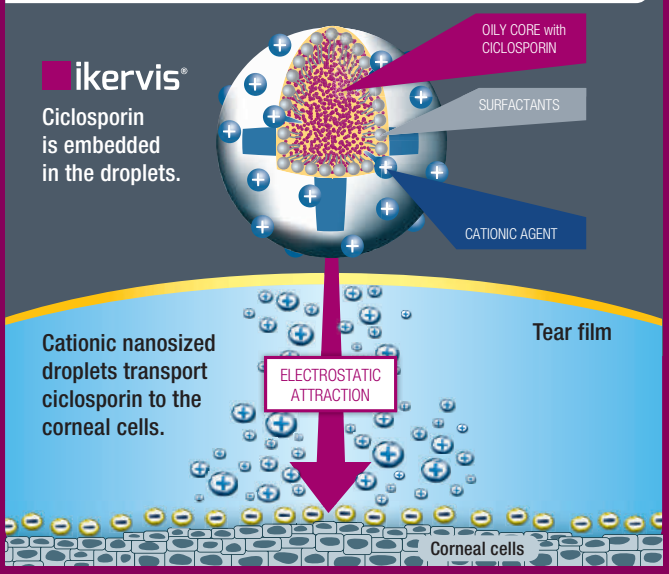


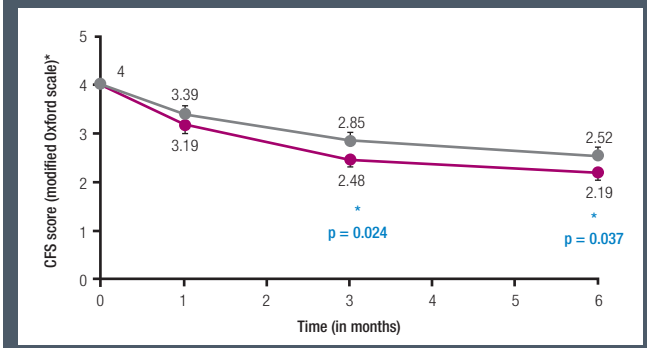
FIGURE 2. Evaluation of keratitis using modified Oxford scale

The two groups were comparable in terms of age, gender, menopausal status, Sjögren's syndrome and severity of keratitis. The median grade of CFS for both groups was 4. The OSDI was much higher than the theoretical threshold (61.44 for the Ikervis® group vs. 58.77 for the vehicle group), confirming the severity of subjective symptoms at the time of inclusion. The Visual Analogue Scale (VAS) score was around 55 for both groups. Schirmer test scores were low for both groups (under 4). Break-up time of the lachrymal film was a little over 3 seconds for both groups.

The primary criterion was a composite of the CFS score and OSDI questionnaire. A patient was considered a responder if, at month 6, the CFS score was reduced from level 4 to level 2 or below and the OSDI was reduced by 30% compared to baseline. The proportion of patients achieving ≥2 grades of improvement in CFS and a 30% improvement in symptoms (OSDI) by month 6 was 28.6% with Ikervis® vs. 23.1% with vehicle, albeit not statistically significant (p=0.326) (primary endpoint).

Additionally, the assessment of corneal damage showed greater improvement with Ikervis® vs. vehicle in mean adjusted CFS change from baseline to month 6 (-1.764 vs. -1.418, p=0.037) (**Figure 3**), while the mean OSDI change from baseline was -13.6 with Ikervis® and -14.1 with vehicle at month 6 (p=0.858).

FIGURE 3. CFS score of patients on Ikervis® vs. vehicle



* 1 CFS score corresponds to at least 3.16 fold more dots on the cornea

The composite CFS-OSDI score was admittedly optimistic and very hard to achieve in real life. Consequently, statistical threshold was not reached because of the restrictive composite criteria. It is important to note that 100% of patients at study inclusion had a CFS grade of 4. Although there was a statistically significant difference between the Ikervis® and vehicle group of around 0.35 in the Oxford scale, the real question remains: is this clinically significant?

It is important to remember that the modified Oxford scale is a visual logarithmic scale.[3] This means that one additional grade of staining corresponds to at least 3.16 fold less dots on the cornea. This means that compared with vehicle, Ikervis® significantly reduced keratitis at 3 and 6 months by around 50% more punctate dots in the cornea. Post-hoc analysis also showed that at 6 months, 34.6% of patients in Ikervis® group moved from CFS level 4 to below level 1 (vs. 14.4% in vehicle).

There was a reduction in ocular surface inflammation assessed by human leukocyte antigen-D related expression in favor of Ikervis® at month 6 (p=0.021). Ikervis® significantly reduced laboratory signs of inflammation of the conjunctiva after only one-month instillation compared to vehicle. The main adverse event was instillation site pain (29.2% vs. 8.9% in the Ikervis® and vehicle groups, respectively), which was mostly mild.

Results from the SANSIKA study demonstrated that Ikervis® was found to be well tolerated and effective in improving corneal damage and ocular surface inflammation. These results also confirmed the positive benefit–risk profile of this new formulation of cyclosporine A cationic emulsion for the treatment of severe keratitis in DED.

Clinical Benefits Of 0.3% Hyaluronic Acid in Dry Eye with Ocular Surface Damage

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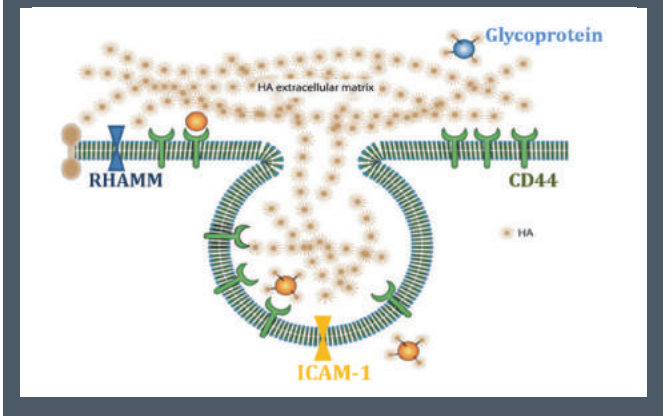
Hyaluronic acid (HA) has been used in the field of ophthalmology for over three decades. Its structure is very simple but once it is secreted into the extracellular matrix (ECM), HA can bind to other proteins with different functions. HA also has different molecular weights, giving it various functions. These factors can make the biology of HA more complex. It has different receptors on the surface of the cell membrane, the most well-known of which are CD44, as well as HA-mediated motility receptor (RHAMM) and intercellular adhesion molecule-1 (ICAM-1) (**Figure 4**). When HA binds to different receptors, it can activate different signaling pathways such that it can pass into the cells, thereby performing various biological functions. It has a hygroscopic

to Dry Eye Treatment

FIGURE 4. Schematic drawing of HA in extracellular matrix



nature, viscoelastic properties, bacteriostatic effect, biocompatibility, anti-inflammatory functions, anti-edema effect, non–antigenicity, and anti-oxidant properties.

EVIDENCE FOR HA BENEFICIAL EFFECT ON THE OCULAR SURFACE

HA and CD44 mediates signaling in keratinocytes.[4] HA binds to CD44 receptor, which can trigger different signaling pathways, mainly Rho-kinase (ROK) and protein kinase N (PKN), eventually leading to keratinocyte growth and survival, migration, cell-cell adhesion, and differentiation. HA plays a major role in the re-modelization of the ocular surface microenvironment in dry eye.

Several studies have shown that HA prevents benzalkonium chloride (BAC)–related cell damage. BAC is a commonly used preservative in eye drops. The studies found that HA prevented BAC–induced DNA damage; the hydroxyl in HA absorbs BAC–induced reactive oxygen species (ROS); HA prevents BAC–induced cell apoptosis; and HA inhibits activation of the P2X7 receptor.[5–7]

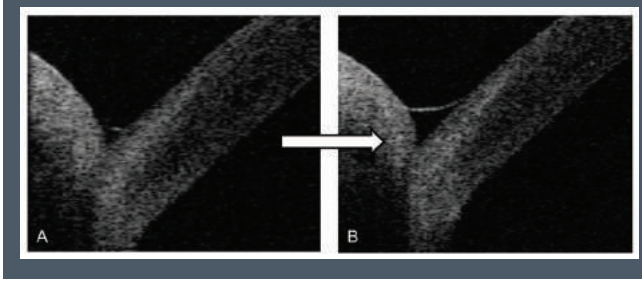
HA can also prevent BAC–induced microvilli damage in the cornea caused by long-term glaucoma treatment. HA promotes barrier function of the corneal epithelium.[8] 0.3% HA prevented BAC–induced goblet cell loss in a rabbit model.[9] HA promotes corneal epithelial wound healing,[10] and protects corneal epithelial cells in patients with dry eye syndrome.[10–12] Finally, HA and fibronectin have a synergistic effect in stimulating corneal epithelial migration.[12]

OVER THREE DECADES OF EXPERIENCE WITH HA USE IN DED

HA has been used clinically in the treatment of dry eyes over the past 32 years. It is available in several concentrations (0.1%, 0.15%, 0.18%, 0.3%, 0.4%) and formats (eye drops and hydrogel, with or without preservative) in single– or multiple–use package.

HA has a significantly longer mean half-life on the ocular surface (321 seconds) than HPMC (44 seconds) or polyvinyl alcohol (39 seconds).[13] Compared to 0.3% hydroxypropyl methylcellulose (HPMC)/0.1% dextran, HA provides a significantly ($p<0.05$) greater increase in non–invasive tear film break-up time (NIBUT) in patients with evaporative tear–sufficient dry eye due to lipid tear deficiency (LTD).[14] HA can increase tear film thickness (TFT) in healthy subjects for as long as 30 minutes,[15] and has been shown to effectively improve tear film stability in dry eyes for up to two hours after instillation.[16] HA can also greatly increase tear meniscus volume (TMV) in healthy subjects (**Figure 5**).[17]

FIGURE 5. HA can increase tear meniscus volume (TMV)



PRELIMINARY RESULTS OF A CHINESE MULTI-CENTER CLINICAL STUDY

The Eye Institute of Xiamen University and six other major Chinese ophthalmic facilities are conducting a self-controlled, open, multicenter clinical study to determine the efficacy of 0.3% sodium hyaluronate (SH) in patients with mild to moderate dry eyes. The total participants enrolled to date is 128 patients, about 58% of the target sample size. The patients were given 0.3% SH six times a day for 14 days, after which clinical and laboratory assessments were done. They then received 0.3% SH six times a day for another 14 days, and clinical and laboratory assessments were repeated.[18]

Evidence gathered so far points to a consistent picture indicating that 0.3% SH improves dry eye symptoms and vision quality, reduces conjunctival inflammation, increases tear film stability, promotes epithelial wound healing, and induces normal differentiation of goblet cells.[16]

KEY CLINICAL PRACTICE POINTS FROM THE PANEL DISCUSSION

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- Ikervis® is the only high concentration cyclosporine eye drop approved for treatment of severe keratitis with dry eye. It is administered as 1 drop per day into the affected eye or eyes before sleeping. Ikervis® treatment response must be reassessed at least every 6 months.
- The effectiveness of Ikervis® can be attributed to the interaction between the positive charge of its vehicle—a cationic emulsion, and the negatively charged ocular surface. Together, there will be an increase in the surfactant effect of the treatment resulting in an increase of cyclosporine delivery into the epithelial cells.
- Treatment discontinuation should be considered in patients that demonstrate significant reduction in keratitis after 12 months of cyclosporine treatment. These patients should be assessed and treatment resumed if relapse occurs. Patients with moderate reduction of keratitis should be treated with cyclosporine for longer than 12 months.
- Cyclosporine treatment as add-on to tear substitutes may be considered in patients who experience dry eye after LASIK surgery.
- Hyaluronic acid is the naturally occurring form in the body while sodium hyaluronate is the active ingredient in eye drops. Sodium hyaluronate, which has a high molecular weight, can be cleaved into smaller, lighter molecules. High- and low-molecular weight sodium hyaluronate have different biological functions. Further research should be done in this area.

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