Hyaluronan: A Review of its Properties, Ophthalmic Uses and Research

Hyaluronan, which is found throughout the body, may have a protective effect against oxidative damage to cells.

By Marjorie Rah, OD, PhD

Many scientists and engineers have discovered that rather than attempting to recreate the wheel to develop a new tool, it is easier, and often more efficient, to simply improve upon products or systems that already exist. Often, nature is the inspiration for these innovative ideas. For instance, nocturnal helmet geckos have been found to have excellent night vision due to a series of distinct concentric zones of different refractive powers.1,2 Studies on the gecko eyes are used to develop more effective cameras and multifocal contact lenses.1,2 Another example is the development of synthetic red blood cells at the University of California – Santa Barbara in collaboration with the University of Michigan.3,4 The synthetic red blood cells not only mimic the characteristics of natural red blood cells, but can be used as carriers for therapeutic and diagnostic agents. Nature is full of inspiring products ranging from airplane wings inspired by birds, cooling systems developed to mimic termite habitats, immune systems for computers patterned after vertebrate immune systems and healthcare products inspired by nature.5,6 For example, artificial limbs and joints are inspired by the natural biological structures they are intended to replace.

Similar inspirations are evident in ophthalmic products. Many products that mimic natural biological structures already exist. Some examples can be found in the area of intraocular lens implants (IOLs). The Crystalens (Bausch + Lomb) is an accommodating IOL designed to mimic the natural accommodative ability of the crystalline lens. Similarly, and of interest in this article, are the components found throughout the body and nature that mimic the natural tears and can be used for treatment of dry eye and to increase comfort and wearing time with contact lenses.

Contact lens companies have attempted to mimic the ocular surface in an effort to improve comfort and wettability. Adding polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) into contact lens materials to improve wettability and improve comfort are examples.7 Similarly, wetting
agents such as surfactants (for example, poloxamine and Tetronic 1304), demulcents (for example, carboxymethylcellulose), and hyaluronan (HA) are added to contact lens products to enhance the wettab-
ility and comfort of them.7 It is the latter that is of interest here. HA can be found in rewetting drops, such as Aquify Long Lasting Comfort Drops (Ciba Vision) and Blink Contacts Lubricating Eye Drops (Abbott Medical Optics).

HA, a naturally occurring glycosaminoglycan, is found throughout the human body — in the connective tissue of the skin, inside the umbilical cord, in synovial fluid in joints and in the eye.8-10 More specifically with regard to the eye, it is found in the vitreous, lacrimal gland, cornea, conjunctiva and in tear fluid.8-12 It is thought to have anti-inflammatory properties and to play a role in wound healing.11-13 In addition, it is thought to have a protective effect against oxidative damage to cells because of its ability to inhibit free radicals.11-13

Developed for ocular surgery, Healon (Abbott Medical Optics), containing 1% sodium hyaluronate, was designed as a vitreous replacement. Eventually, it was also used during cataract surgery to protect the corneal endothelium and to provide better graft transparency in corneal transplant surgeries.16

The random coil structure of HA results in unique water-retention properties and viscoelasticity. When used in solution in eyecare products, HA is highly viscous, but changes in temperature, pH and shear rate lower the viscosity.8,17 These changes in shear rate are achieved with blinking. When the eye is open, the HA is more viscous and coats the surface of the eye without draining, which improves the tear break-up time.8,14,15,18 When the eyelids blink, the viscosity is reduced resulting in the HA spreading across the eye for a smooth, lubricating blink. These qualities, in combination with its affinity for water, were a classic biological inspiration for producing artificial tears. As a result, it was a natural progression for the molecule to make its way from the operating room to the artificial tear bottle.

Several studies have been conducted using HA in artificial tears to determine its effect on dry eye signs and symptoms (Table 1).10,19-22 These studies have included patients with mild to severe dry eye, as well as patients with such corneal disorders as epithelial corneal dystrophy, contact lens-induced irritation, ocular pemphigoid, filamentary keratitis and neurotrophic keratitis.10, 19-22 Most of the studies have

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**Table 1**

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>TREATMENT</th>
<th>RESULTS</th>
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<tbody>
<tr>
<td>Stuart JC, Linn JG (1985)</td>
<td>0.1% sodium hyaluronate</td>
<td>Patients reported relief of dry eye symptoms</td>
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<td>Objective improvement in corneal staining</td>
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<td>Sand BB, Marner K, Norn MS (1989)</td>
<td>0.1% sodium hyaluronate, 0.2% sodium hyaluronate, placebo</td>
<td>No significant difference in Schirmer testing, tear break-up time and rose Bengal staining, between 0.1% HA and the placebo</td>
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<td></td>
<td>Significant difference in objective testing between 0.2% HA and placebo</td>
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<td></td>
<td></td>
<td>The majority of patients preferred treatment with HA</td>
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<tr>
<td>Hamano T, Horimoto K, Lee M, Komemushi S (1996)</td>
<td>0.05% sodium hyaluronate, 0.1% sodium hyaluronate, 0.3% sodium hyaluronate, vehicle</td>
<td>No significant effect on tear break-up time noted for the vehicle or the 0.05% concentration of HA</td>
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<td>Break-up time was significantly delayed with 0.1% and 0.3% HA at all measurement times up to three hours</td>
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<tr>
<td>Johnson ME, Murphy PJ, Boulton M (2006)</td>
<td>0.1% sodium hyaluronate, 0.3% sodium hyaluronate, 0.9% saline</td>
<td>A significant improvement in break-up time up to six hours for both 0.1% and 0.3% HA, but not for saline</td>
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<td>0.3% had greatest effect on improvement of symptoms across the entire 6-hour time period of the study</td>
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<tr>
<td>Prabhasawat P, Tesavibul N, Kasetsuwan N (2007)</td>
<td>0.18% sodium hyaluronate, 0.3% hydroxypropylmethylcellulose/0.1% dextran</td>
<td>Improvement in break-up time was significantly greater in the HA group at 30 and 60 minutes</td>
</tr>
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focused on results from subjective questionnaires and objective measurements of tear break-up time as the primary outcomes, but other dry eye test results (phenol red thread test, tear meniscus height, non-invasive tear break-up time, bulbar hyperemia, fluorescein and lissamine green staining of the ocular surface) have also been studied. Studies show a variety of results with regard to the effect of HA in artificial tears (Table 1). As these studies were not head-to-head trials, a comparison of results should not be made, but it can be noted that these studies did demonstrate a positive effect of HA.

Although the literature on the topic is sparse, there are some notable contact lens studies utilizing HA. Itoi and colleagues evaluated the effect of HA on 3 and 9 o’clock staining in rigid gas permeable contact lens wearers. Patients were randomized to HA or artificial tears and were followed for both subjective symptoms and objective clinical signs. Although no significant differences in subjective symptoms were found, significantly less objective signs (corneal staining and conjunctival hyperemia) were noted in the group using HA drops.

In addition, studies have been conducted in which HA has been incorporated into hydrogel and silicone hydrogel lens materials to determine the effect on protein adsorption. The hyaluronic acid was incorporated as a wetting agent in the soft contact lenses. Incorporating the cross-linked HA into hydrogel lenses significantly decreased protein adsorption of lysozyme, albumin and the larger protein IgG. Similarly, incorporating cross-linked HA into silicone hydrogel materials significantly decreased the uptake of lysozyme. Most recently, hydrogel lenses have been designed to release HA at a controlled rate for therapeutic delivery of HA to the eye, to improve the wettability of contact lenses and treat the symptoms of dry eye.

It is evident from the products and studies mentioned above that natural tears serve as a biological inspiration for HA-based ophthalmic uses. HA is found throughout the body and can be used to mimic the natural tears in such products as artificial tears, contact lens rewetting agents and as a wetting agent incorporated into contact lens care products or contact lens materials.

These advancements in contact lens care and design hopefully will lead to better comfort for our contact lens patients and may reduce the number of patients who limit wearing time or discontinue contact lens wear as a result of ocular dryness and discomfort.

References

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