CSCRS Meeting Report

Clinical & Refractive Optometry is pleased to present this Report from a presentation given by Dr. Steve Arshinoff at the 2013 Canadian Society of Cataract and Refractive Surgery (CSCRS) Meeting in Toronto in which he discussed viscoadaptive artificial tears as an efficacious, safe option for the treatment of dry eye.

A New Modality for the Treatment of Dry Eye Syndrome

Steve A. Arshinoff, MD, FRCSC

Introduction

Dr. Arshinoff began his presentation by outlining the topics he would be discussing, namely: a review of past and current choices for the treatment of dry eye; the variety of treatment modalities available for dry eye syndrome; rheology; ophthalmic viscosurgical device (OVD) properties; and the composition and behavior of viscoadaptive eye drops.

Evolution of Dry Eye Treatment Approaches

Dr. Arshinoff referenced the 2007 International Dry Eye Workshop at which Committee members developed a framework for the definition, classification and mechanisms of dry eye (Fig. 1).

He noted that dry eye has become somewhat of a "catch-all" term whose underpinnings are the result of either high evaporation or low lacrimal flow. Prior to the development of Restasis® (Allergan, Markham, ON), a form of artificial tears, pharmaceutical companies responded by providing watery artificial tears, replacing water, or by decreasing evaporation.

There are currently three types of eye drops available on the market: anti-inflammatories, such as Restasis, and then replacing deficiency, as with HypoTears® (Novartis Dorval, QC), TheraTears® (Advanced Vision Research, an Akorn company, Ann Arbor, MI) and Tears Naturale® (Alcon, a Novartis company, Mississauga, ON), or reducing evaporation.

Dr. Arshinoff cited Alcon's development of successive iterations of eye drops based on a shift in direction from replacing water to preventing evaporation, a direction that merits further examination. This past decade, for example, has seen a product evolution from Systane® (Alcon, a Novartis company, Mississauga, ON) to Systane Ultra, to Systane Balance, to gel drops.

Rheology: Studying Fluid Behavior

Dr. Arshinoff presented an explanation of rheology, the science of how fluids respond to forces, or the mechanics of fluids, and how it works in the devices ophthalmologists use.

The study of rheology involves concepts relating to viscosity, elasticity and the cohesion/dispersion continuum. He pointed out that rather than a single line, it is an endless variation of whether a substance is cohesive or dispersive (Fig. 2).

Dr. Arshinoff stated that there are four different ways fluids can respond to forces, the first of which is Newtonian, which means that no matter how much force you expose the fluid to, its viscosity remains the same (Fig. 3).

The other extreme interest is plastics, whose name derives from the plastic curve: plastic infers that when a substance flow very quickly, it is very fluid; but when it flows very slowly, it becomes solid.

Imagine, suggested Dr. Arshinoff, trying to use a plastic in ophthalmology. The substance is put in the eye and it turns solid, which could make surgery difficult. As a result, what is used instead are devices called pseudoplastic. In Figure 2, the blue line represents pseudo-plastic which means that, like a plastic under high forces going through a syringe, it has very low viscosity. However, when sitting in the eye, the viscosity increases — reaching what is called a limiting or a zero-shear viscosity — and then levels off. The graph levels off and does not go higher than whatever the zero-shear viscosity is. The corollary is, the only useful number for any viscoelastic used is a zero-shear viscosity, because the other viscosities depend on how fast the substance is being moved.

The graph shows the range of pseudoplastic OVDs used, although the HPMCs are not very pseudoplastic. Note that the top red line depicts i-Visc® Phaco (I-MED Pharma, Montreal, QC) as "almost plastic."

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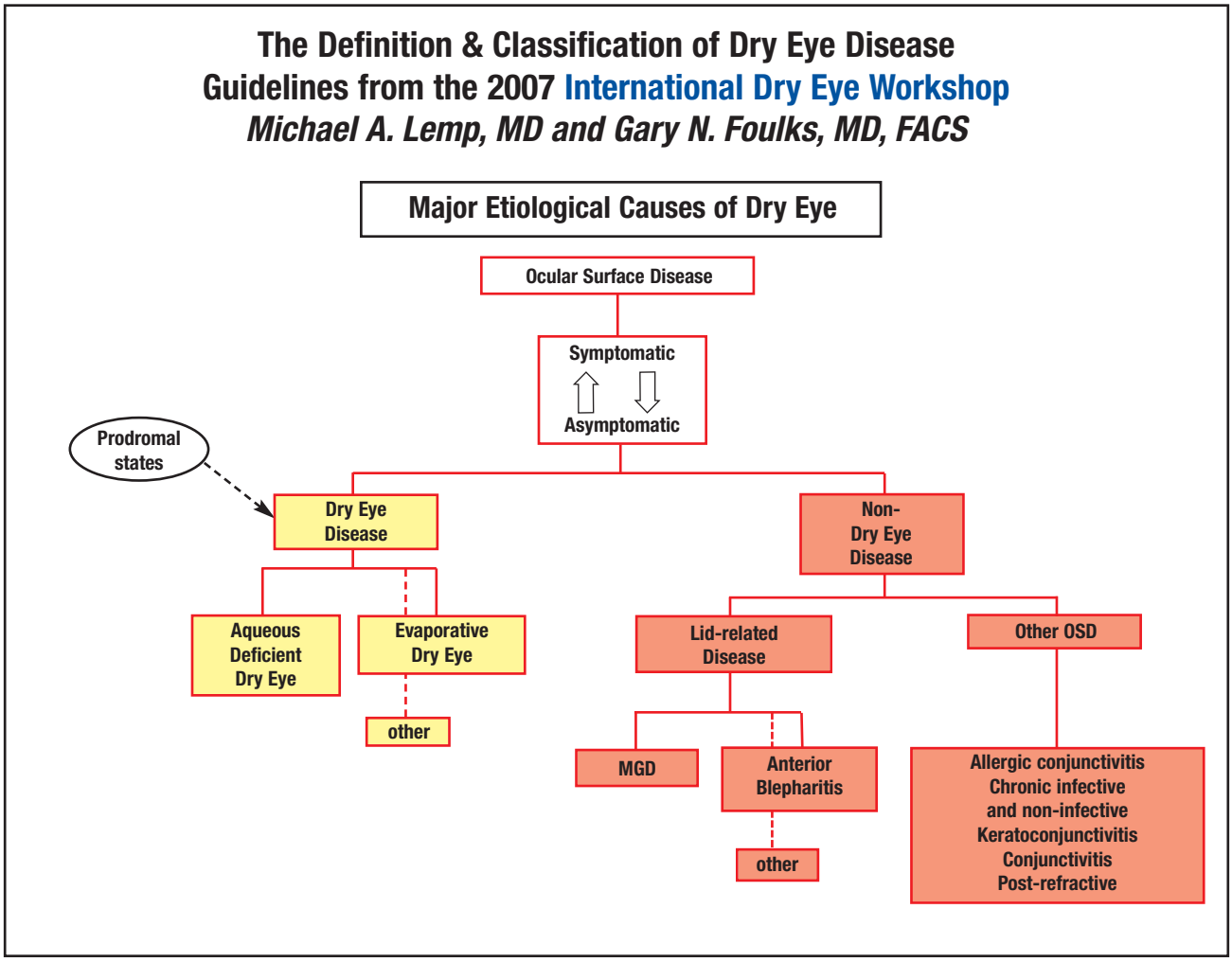

Fig. 1 Etiology of dry eye

The last of these four is dilatant, as indicated by the pale blue line in Figure 2. Dilutant is the opposite of pseudoplastic, meaning that the more force it is exposed to, the more viscous it becomes.

Newtonian Solutions in Ophthalmic Products

An example of ophthalmic viscous Newtonian solutions are the low pseudoplasticity surgical ophthalmic viscoelastic devices (OVDs), such as i-Cel® (I-MED Pharma, Montreal, QC), OcuCoat® (Bausch & Lomb, Vaughan, ON) and Cellugel® (Alcon, a Novartis company, Mississauga, ON), the two bottom lines there, as shown in Figure 2. The line representing these is more or less horizontal, meaning that the viscosity does not change with a change shear rate, except for the very end, where the levels descend. What this indicates is that if you are going to use an HPMC OVD, it is going to behave more or less the same in the eye, irrespective of shear rate. The surgeon would have to push down very hard on the syringe to expose it to a lot of force, to go through a canula. For this reason, they are equipped with larger canulas than other OVDs.

In terms of artificial tears, examples that are more or less Newtonian include: HypoTears, Tears Naturale, Systane, GenTeal® (Alcon, a Novartis company, Mississauga, ON), and Refresh® (Allergan, Markham, ON).

Non-Newtonian solutions are used in intraocular surgery, most of which are pseudoplastic (Fig. 4). Highly pseudoplastic ones, which means they have a high viscosity at low shear, and a low viscosity at high shear, have a limiting zero-shear viscosity. Examples of this are Healon®, Healon GV® (Abbott Medical Optics, Markham, ON) and i-Visc.

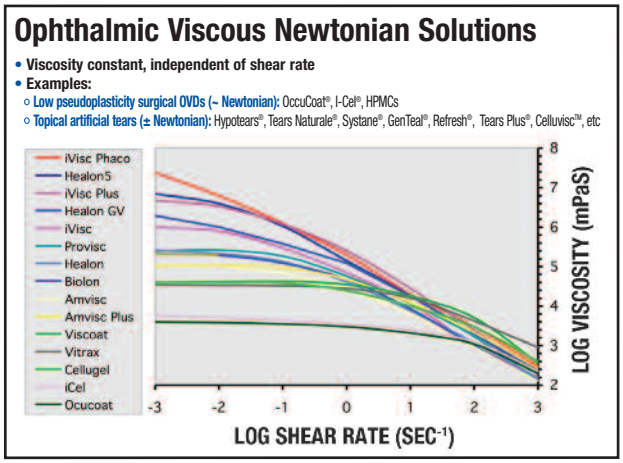

Fig. 2 Newtonian ophthalmic solutions: A continuum of viscosity.

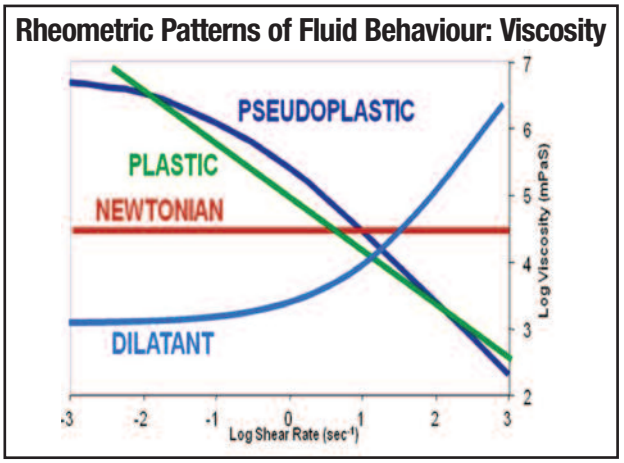

Fig. 3 Fluid behavior in response to forces.

"Viscoadaptive": What It Means and What It Does

Artificial tears containing hyaluronic acid — a long enough chain that behaves like a pseudoplastic material — were developed as far back as twenty years ago; Hylashield was the first of these.

Dr. Arshinoff stated that three terms — viscous, elastoviscous and viscoadaptive — are used to describe the various treatments for dry eye. He noted that the term "viscoadaptive" may be confusing to some practitioners; for example: what does viscoadaptive mean in terms of OVDs used in cataract surgery?

Viscoadaptive signifies that the behavior of the OVD changes from a highly viscous cohesive — like a Super Healon or Super Healon GV — to a pseudodispersive. However, Dr. Arshinoff pointed out, it is not truly dispersive: it becomes a fracturable solid. Both iVisc phaco and Healon 5, when they are absolutely stationary, can behave like solids. The way you make it behave like a solid is you change the ambient environment inside the anterior chamber. So if you increase your flow rate of fluid in the anterior chamber, you are exposing the OVD to turbulence.

The very viscous OVD will behave like a solid and will fracture like a solid. The term viscoadaptive was designed to mean that we can change our flow rate in the eye and make the OVD behave like a dispersive, but not through the same mechanism. You can take Healon GV or iVisc, though, and make it behave in cataract surgery either like Super Healon GV or as a dispersive, because it will fracture apart with high turbulence.

Flow rates of 10 to 45 are used. In Figure 2, Viscoat® (Alcon, a Novartis company, Mississauga, ON) behaves as a dispersive throughout those flow rate settings; and Healon GV behaves as a cohesive across those flow rate settings. However, Healon 5 will behave initially as a cohesive and then has a phase change and behaves as a solid with flow rates exceeding 25.

Composition and Behavior of Viscoadaptive Artificial Tears

In artificial tears, "viscoadaptive" refers to an elasto-viscous solution. There are chains of hyaluronic acid that are not as long as those that would be used in an intraocular OVD. When these chains are exposed to the force of blinking, they are more elastic than they are viscous. In terms of blinking, when you blink with an elastic in your eye, you blink and it compresses; it does not go anywhere. When you open your eye, it comes back and stays there, because it is acting like a spring. This was the first concept in developing a viscoadaptive tear, which is not really viscoadaptive.

The second concept is to add something to the tear which will make it behave differently again, which resulted in glycerol, a small molecule, being added. Because the hyaluronic acid absorbs all the water, and there is no free water in the solution, when it is compressed, it excludes the glycerol. As a result, as soon as you blink with these tears, the glycerol comes to the surface, reinforcing your lipid layer and providing better tear lubrication.

Dr. Arshinoff noted that it is not truly viscoadaptive; it is a different interpretation of viscoadaptivity. i-drop® (I-MED Pharma, Montreal, QC) is the first product of its type on the market, made of high-molecular weight hyaluronic acid and glycerol; it is an elastoviscous solution of hyaluronic acid. Glycerol is excluded during blink, thereby lubricating the tears during the blinking process (Fig. 5).

An additional advantage is that every human cell has hyaluronic acid binding sites, so when you take these

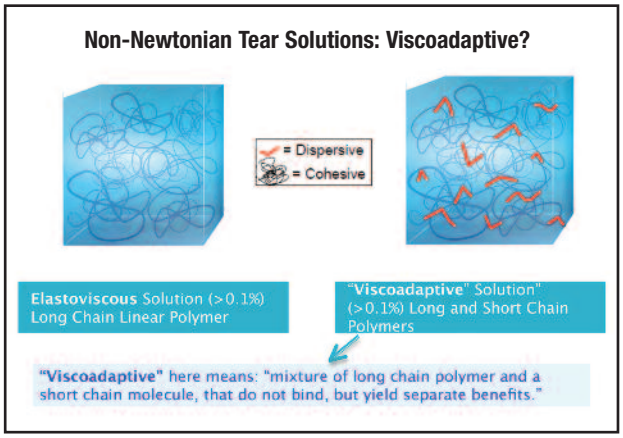

Fig. 4 Dispersive and cohesive properties of non-Newtonian tear solutions.

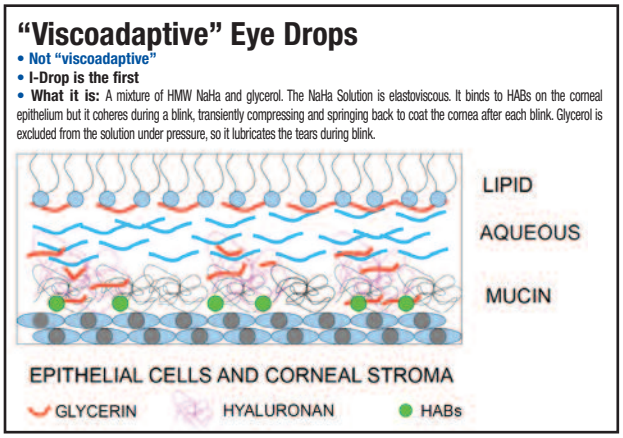

Fig. 5 Viscoadaptive eye drops mode of action.

chains of hyaluronic acid and put it on your cornea, it adheres to the corneal surface. Therefore, when blinking it remains fixed: it is stuck to the cornea. Together with the water layer and the glycerol that moves in and out with blinking, the formula represents the potential for an improved artificial tears product.

In 2003, the first viscoadaptive eye drop was launched in Canada, followed by Oasis TEARS® (Oasis Medical, Glendora, CA) in 2009 — the first viscoadaptive hyaluronan-based eye drop launch in the United States. In 2013, i-drop Pur and i-drop Pur Gel (I-MED Pharma, Montreal, QC) were approved as the first non-preserved multidose viscoadaptive eye drops.

Patient Benefits of Viscoadaptive Artificial Tears

Dr. Arshinoff summarized his presentation by describing the potential advantages of i-drop artificial tears. i-drop Pur artificial tears are pseudoplastic elastoviscous tears, with a second molecule to increase lubrication. They exhibit polymer crowding, so there is no free water. In addition, they are blink responsive in that they are elastic, so they stay in the eye. They adhere to the cornea and the blink energy allows them to spread better over the eye. It releases glycerol to increase lubrication and it lasts longer than other drops in the i-drop family of products. Dr. Arshinoff mentioned that as it launched only one year ago, there is not yet substantial clinical experience to report.

The proposed patient benefits are: enhanced protection of the cornea; prolonged residence time on the cornea because of the binding sites; smoother to blinks; higher degree of patient comfort; very good corneal hydration; and less tear evaporation, which seems to be the direction in which other companies are moving in developing their eye drops. ❑