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LISTEN, LOOK, ACT: Making Sense of the Emerging Science in Dry Eye Disease

An evidence-based perspective on the impact and management of chronic dry eye disease.

BY JOHN A. HOVANESIAN, MD

Dry eye disease (DED) symptoms were estimated to affect millions of individuals in the United States,[1,2] and yet there is evidence that it may be underestimated.[3-5]

DED is one of the most common reasons why patients visit eye care professionals.[4] Moreover, in a 2008 Beaver Dam Offspring Study (BOSS) that evaluated 3,275 patients 21 to 84 years of age, it was estimated that as much as 14.5% of the study population had symptoms consistent with DED,[1] which in real numbers represented approximately 30 million individuals, based on the estimated total population in the United States between 20 to 84 years of age in 2008, according to the US Census Bureau, Current Population Survey, Annual Social and Economic Supplement, 2008.[2] Additionally, in a study of 136 patients that looked at the incidence of dry eye in patients age 55 and older who were scheduled to undergo cataract surgery, 77% of eyes presenting for cataract surgery had positive corneal staining, but only 22% of patients had a previous diagnosis of dry eye disease at baseline.[6] However, it is known that DED signs and symptoms do not always correlate.[7] As well, signs and symptoms may fluctuate over time.[8]

DED can affect the perception of visual quality, interrupt daily activities,[4] and negatively impact work productivity and psychological health.[9,10] In my opinion, despite the fact that DED has a very real impact on the health of the ocular surface, has potential to result in refractive surprise after cataract surgery, and may negatively affect patients' daily lives, some patients use interventions targeted to alleviating symptoms rather than addressing an underlying disease process.

Ultimately, I feel that what these findings suggest is that a different approach to diagnosis and treatment may be needed. There are also treatment strategies that address both signs and symptoms of DED. But, how can clinicians achieve the holy grail ideal of early recognition of DED and timely intervention?

DED: IMPACT ON THE OCULAR SURFACE

There are a few important facts about DED that have emerged over the past decade. It is now thought that DED is chronic and may be progressive.[11-13] The proliferation of the use of digital devices in the modern era has added an additional desiccating stress to the list of known risk factors associated with DED, including contact lens use, environment and diet, comorbidities and certain medications, advancing age, and ocular surgery.[4] What is interesting, though, in my opinion, is how these various risk factors may interact to compound stress on the ocular surface. In addition, screen time and contact lens wear are potential risk factors for DED, which is becoming more common among younger individuals.[4] There is evidence that age is a more consistent risk factor for DED, although this may vary based on diagnosis. Dry eye prevalence may increase with age.[4] In summary, I believe that there is inherent truth in the paradox that, if you have seen one dry eye patient, you have only seen one dry eye patient. That is, in my opinion, each

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individual has his or her own risk profile in terms of developing the signs and symptoms of DED.

In my opinion, this notion of individualized risk profiles associated with DED may explain the evolving understanding of its etiology and ultimately how it should be treated. The classic model that grouped patients according to aqueous deficient versus evaporative, with treatment directed at the supposed cause, in my opinion, does not align with what has been learned about the multifactorial nature of DED. Although the majority of DED is evaporative,[11] it has been estimated between 30% and 70% of patients have a mixed etiology, but these are based on estimates made by clinicians using clinical judgment.[14,15] However, the two types of DED may share a pathophysiological pathway characterized by tear film instability, hyperosmolarity, and inflammation that may blur the distinction between underlying aqueous deficient and evaporative etiologies (Figure 1).[11]

In my opinion, the implications for understanding DED and how it affects the health of the ocular surface, regardless of etiology, may have important consequences for how it is diagnosed. The clinician can listen for clues in what patients relay. Unexplained fluctuation in visual quality can be a tip-off, but so, too, are reports of interruptions to daily activities, such as difficulty with driving and reading.[4] In my opinion, based on these symptoms, the clinician can then begin the evaluation with a mindset of looking for DED risk factors and signs. Finally, if DED is identified, intervention can be started to interrupt the disease cycle—and acting on behalf of patients may be the most important thing.

THE PROMINENCE OF INFLAMMATION IN DED

It is important to note that the evolved understanding of DED etiology and pathophysiology, in my opinion, has not complicated the treatment approach. On the contrary, it is now well known that tear film hyperosmolarity is an underlying hallmark of the disease, and inflammation may be part of its pathophysiology.[7]

At the cellular level, a key trigger of inflammation in DED, based on in vitro data, is thought to be binding of intracellular adhesion molecule 1 (ICAM-1), which may be overexpressed in corneal tissue in patients with DED, with lymphocyte function antigen 1 (LFA-1), a cell surface protein found on the surface of T-cells.[16,17] This binding, in turn, can result in T-cell migration to target tissues, T-cell activation, and the subsequent release of inflammatory cytokines. In vitro studies showed that lifitegrast ophthalmic solution 5% (Xiidra; Novartis) blocked the interaction of ICAM-1 and LFA-1, and may inhibit recruitment of activated T-cells and activation of newly recruited T-cells, and the release of proinflammatory cytokines (Figure 2).[18,19] In other words, it is thought that lifitegrast ophthalmic solution 5% targets a source of inflammation that can perpetuate DED. The exact mechanism of action of Xiidra in DED is not known.[18]

Support for the drug's approval by the US Food and Drug Administration comes from a large DED clinical program in support of a prescription therapy. Lifitegrast ophthalmic solution 5% was evaluated for safety and efficacy in four separate 12-week, double-blind, placebo-controlled studies (N = 2,133 total patients),[18] as well as for safety compared to vehicle in a year-long safety study (N = 331).[20] In all four of the initial studies, symptom relief, measured by reductions in Eye Dryness Score, was noted at 6 and 12 weeks after starting therapy, and in two of the studies, reduction in symptoms of eye dryness were seen at the week 2 follow-up in some patients.[18] In three of the four studies, there was

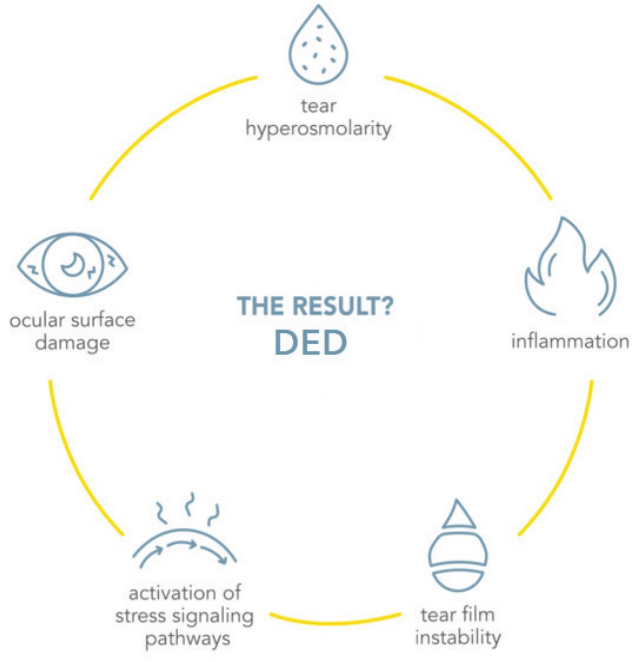

Figure 1. The classical model of characterizing DED etiology as either evaporative or aqueous deficient may be incomplete to explain the multitude of potential inciting factors. On the other hand, new evidence demonstrates that the two types may have a shared disease pathway. Regardless of entry point, tear film instability, hyperosmolarity, and inflammation serve to drive further adverse change in the 'vicious circle' that may blur the distinction between underlying aqueous deficient and evaporative etiologies.[5,11]

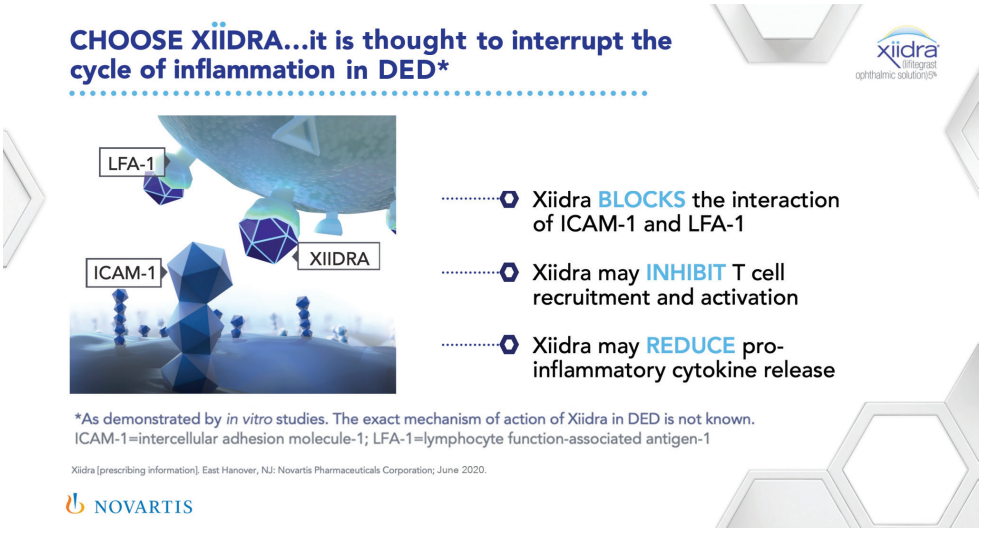

Figure 2. Mechanism of Action of Xiidra.

a larger reduction in ICSS favoring Xiidra in the Inferior Corneal Staining Score, indicating that lifitegrast can also address signs of DED.[18] Meanwhile, in all four studies, plus the longer safety study in which 170 patients were exposed to lifitegrast for approximately 12 months, lifitegrast was shown to be well-tolerated, with the most common adverse reactions, reported in 5% to 25% of patients, being instillation site irritation, dysgeusia (an altered taste sensation), and reduced visual acuity.[18]

From my perspective as a cataract surgeon, we are able to recognize and diagnose DED, initiate treatment, and achieve improvement of signs without significantly delaying surgery. That paradigm expresses to the patient that we take ocular surface health seriously, that we will work to resolve any issues prior to surgery. We have found that, if we set reasonable expectations for patients, both in terms of effectiveness and tolerability of any therapy, there's a better chance the patient will be successful on therapy. ■

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XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical studies of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation Day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data
Animal Data
Lifitegrast administered daily by IV injection to rats, from pre-mating through gestation Day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing five, 400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation Days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation
Risk Summary
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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