By Paul M. Karpecki, OD, FAAO

Rethinking DED Treatment

Dry eye disease is an underestimated disease in need of new treatment options.

Dry eye disease (DED) is a chronic disease that negatively impacts quality of life comparably to other severe diseases.[1] Symptoms of DED such as feeling of dryness, burning, foreign body sensation or pain are often quite debilitating. Moreover, visual function-related manifestations including fluctuating vision with blinking, blurred vision and difficulty with reading despite normal visual acuity are important and underestimated aspects of the disease.[2]

As many as 5-35% of patients visiting eye care professionals report dry eye symptoms, making it one of the most common ocular conditions seen.[3] And although more than 16 million people are diagnosed with DED in the US,[4] only about 10 percent are treated for the disease.

The fact that 90% of people are not being treated for dry eye means they will likely experience ocular surface damage and a significant drop in quality of life. This situation necessitates a closer look at the unique characteristics of DED, and the way eye care has approached diagnosis and treatment of the disease until now. It also begs the question of whether there might be a better way to care for DED patients.

Characteristics of DED

The International Dry Eye Workshop (TFOS DEWS I and II) classifies dry eye into two major categories: 1) aqueous deficient (i.e., keratoconjunctivitis sicca) and 2) evaporative (i.e., tear-lipid deficient).[5] Research has found that around 10% of dry eye patients have a solely aqueous deficient disorder, in which reduced tear production leads to tear film instability, while 60-90% of patients present with predominantly evaporative dry eye, in which an altered lipid layer leads to tear film instability.[6] About 40% of patients have a mixed presentation.

Meibomian glands on the lower and upper lid play an important role as the sole natural source of lipids for the human tear film. Meibum spreads onto the tear film, promoting its stability and preventing evaporation.[7,8] A large number of DED patients have meibomian gland dysfunction (MGD), either by itself or comorbid with aqueous deficiency. Those suffering from DED with imbalanced tear conditions due to significant MGD represent a symptomatic and large population with great medical needs.

Traditional Treatment of DED

Traditional DED treatment has started with water-based artificial tears and topical lubricants. For moderate to severe cases, topical anti-inflammatory medications, including short two to four-week courses of corticosteroids and longer-term therapy of cyclosporine A and lifitegrast, have been used.[9]

Addressing inflammation is a critical component of treating both forms of dry eye disease. However, available therapies for evaporative DED patients are less optimal, as anti-inflammatory medications often don't address the root cause of excessive evaporation. There is a need for more tolerable and faster-acting agents that have fewer to no side effects, or complication risks.

Treating Inflammation Only One Component of Dry Eye Therapy

It's important to remember that inflammation is just one aspect of the various forms of DED. Although it may be one key to slowing progression, in the case of evaporative DED—making up about 86% of DED—clinicians must also treat the underlying obstructed meibomian glands. At the same time, just treating the obstructed glands of patients with evaporative DED without managing inflammation leads to a potentially quicker return to obstructed glands. Both issues must be handled for optimal outcomes.—*Dr. Karpecki*

Overcoming Limitations

The significant gap between diagnosed and effectively treated patients, as well as the unsatisfying treatment options available for patients require a rethinking of underlying DED mechanisms. It's clear that new therapies are needed.

In response to the need for new DED therapies, Novaliq is developing two topical products for commercialization in the US. Both are based on the company's proprietary water-free EyeSol® technology.

Due to their water-free characteristics, EyeSol® products are preservative- and surfactant-free, and designed to greatly improve tolerability compared with traditional water-based drugs. CyclASol® and NOV03 potentially offer new treatment approaches for both DED segments to improve patients' quality of life.

CyclASol®

CyclASol® 0.1% (cyclosporine A 0.1% in perfluorobutylpentane) is intended as a treatment for patients with moderate to severe DED with an inflammatory component. The use of perfluorobutylpentane as a vehicle for cyclosporine is designed to obviate the need for a preservative, enhance the stability and bioavailability of the active ingredient, and improve comfort.

In the Phase IIb/III ESSENCE study, a multicenter, double-masked trial conducted in the United States, cyclosporine A 0.1% in perfluorobutylpentane met its primary endpoint of change in total corneal fluorescein staining from baseline to week four.[10] A statistically significant improvement in corneal fluorescein staining compared with the vehicle

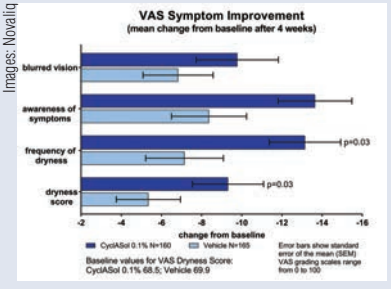
was seen as early as two weeks, and maintained at four, eight and 12 weeks. ESSENCE also significantly met the prespecified symptom endpoint of VAS Dryness Score after four weeks, with a p-value of 0.03. The study included 328 randomly selected patients.

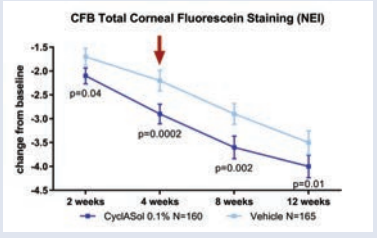
Novaliq believes that CyclASol® 0.1% holds the promise of harnessing cyclosporine A's full potential for the first time in the treatment of DED treatment. It holds the potential to demonstrate the superior benefits of a water- and preservative-free multi-dose formulation, and could enable clinicians to treat more patients suffering from predominantly aqueous deficient DED.[10] This potential is significant because this is not just a higher concentration of cyclosporine A, but rather a vehicle that completely changes how we address the disease in terms of efficacy.

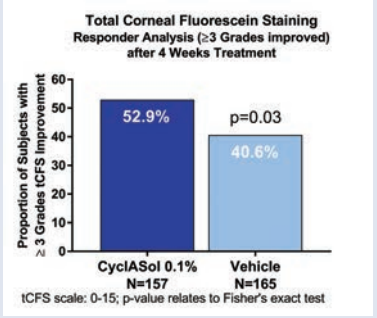
Notably, the drug's water-free nature is designed to result in one of the most comfortable and tolerable dry eye prescriptions we've seen to date. The comfort scores and lack of burning upon instillation in the Phase IIb/III study were remarkably low. This is a very comfortable drop; its water-free characteristics not only help with solubility, but especially with tolerability.

ESSENCE Findings.
Data from the ESSENCE trial.

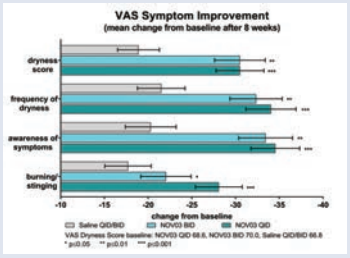
Images: Novaliq

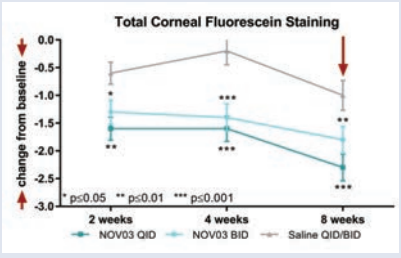






SEECASE Findings. Data from the SEECASE trial.





NOV03

NOV03, a preservative- and surfactant-free product containing 100% perfluorohexyloctane, is being developed as a treatment for patients with MGD-associated DED. Studies show that it helps stabilize the tear film lipid layer and mitigate excessive evaporation. In addition, it has been shown to penetrate into the meibomian gland and liquefy secretions there, improving the quality of the meibum and tear film lipid layer.

NOV03 was investigated in SEECASE, a Phase II, randomized, controlled, double-masked clinical US trial including 336 patients with predominantly evaporative DED associated with MGD. The enrolled patients were highly symptomatic and had a low tear film breakup time, normal Schirmer's scores, and mild to moderate corneal damage. They were randomized into one of four groups—to use NOV03 two or four times daily, or normal saline two or four times daily.

Topline results showed that the study met its prespecified primary endpoint—a change in total corneal fluorescein staining from baseline to week eight.[10] Compared with the control, both dosing regimens of NOV03 showed statistical superiority. The benefit of NOV03 for ocular surface damage was seen as early as two weeks after treatment initiation. The investigational agent was also associated with statistically and clinically relevant improvement in DED-related symptoms.[10]

I'm very excited about the prospect of NOV03. For one thing, it is being investigated to address the most common cause of DED and targets the meibomian glands. Subjects in clinical trials have experienced improvements in a variety of symptoms and corneal staining against control. I would expect we're going to see a significant improvement in vision. NOV03 is also a very comfortable drop, and I like the fact that it is designed to address meibomian gland secretions.

The Future of DED Treatment

Dry eye is a multifactorial disease with respect to its cause and predisposing risk factors, but also in terms of its process. For example, in evaporative DED, factors include obstructed meibomian glands, inflammation secondary to hyperosmolarity, a biofilm or blepharitis component, and a disrupted tearfilm. Having therapeutic agents that address more than one aspect of the disease process and that target different DED segments is extremely valuable for efficacy of treatment, as well as for patient compliance and satisfaction.

Targeted treatment options currently under investigation such as NOV03 and CyclASol®, based on a water- and preservative-free technology, offer hope that new drugs can provide more patients with a satisfying treatment solution—to improve ocular surface damage and DED symptoms, as well as preserve vision and quality of life.

1. Schiffman RM, Walt JG, Jacobsen G, et al. Utility assessment among patients with dry eye disease. Ophthalmology. 2003;110(7):412-9.
2. Koh S. Mechanisms of visual disturbance in dry eye. Cornea. 2016;35(11):S83-8.
3. McCarty CA, Bansal AK, Livingston PM, et al., The epidemiology of dry eye in Melbourne, Australia. Ophthalmology. 1998;105(6):1114-9
4. Farrand, Fridman, Stillman IO, et al. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. Am J Ophthalmol. 2017:90-8.
5. Foulks GN, Forstot SL, Donshik PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. Ocul Surf. 2015;13(2):pp 118-32.
6. Sharma A, Hindman HB. Aging: A Predisposition to Dry Eye. Journal of Ophthalmology. 2014;781683.
7. Lemp M, Crews LA, Bron AJ, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. Cornea. 2012;31(5):472-8.
8. Nichols K, Foulks GN, Bron AJ, et al. The International Workshop on Meibomian Gland Dysfunction: Executive Summary. IOVS. 2011;52(4):1922-9.
9. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea. 2006;25(8):900-7.
10. Novaliq data on file.

NOV03 and CyclASol are investigational products and not approved, yet.