New Insights and Recent Developments in Dry Eye Disease

A seminar held during the 35th Congress of the European Society of Cataract and Refractive Surgeons (ESCRS 2017) in Lisbon, Portugal and sponsored by Santen Pharmaceutical brought together a panel of prominent experts to review the latest evidence for the treatment of severe keratitis in dry eye disease (DED). The article below features key perspectives drawn from the current therapeutic approaches to severe keratitis with dry eye, results of a randomized phase III study, and clinical experience in Singapore presented by Professor Pierre-Jean Pisella, Professor Andrea Leonardi and Dr Wei-Han Chua, respectively.

Use of cyclosporine A in the management of dry eye disease: The French experience

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Dry eye disease redefined

Since the landmark Tear Film & Ocular Surface Society (TFOS)'s Dry Eye Workshop (DEWS) report published in 2007, the definition, classification and diagnosis of dry eye has been updated and refined, culminating in the 2017 TFOS DEWS II report that reflects the views of more than 150 clinical and scientific experts and their interpretation of the current evidence on ocular surface disease.[1]

According to the newly developed 2017 TFOS DEWS II definition, DED, which affects up to 35% of the world's population,[2] is a multifactorial disease of the ocular surface. DED is characterized by a loss of homeostasis of the tear film. It is accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles.[1] The new definition recognizes that the "loss of homeostasis" of the tear film and ocular inflammation are two central tenets critical to the understanding of the pathophysiology of DED.

Recent advances in the management of dry eye disease

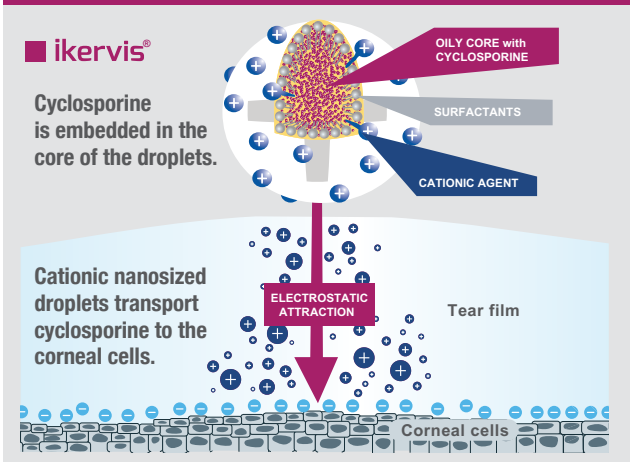
A recent key finding is that DED is not only limited to the corneal epithelium, but also involves the corneal endothelium. The modified Oxford scale provides guidance in evaluating disease severity due to corneal damage.[3] In general, clinical signs alone may be insufficient to reliably diagnose keratitis, and there is a need to take a functional approach by evaluating the impact of severe DED on visual function/quality of life using double pass aberrometry.[4]

A diverse range of management options exists for DED, including tear supplement products and anti-inflammatory agents. Some treatment options such as autologous serum, amniotic membrane, punctal plugs and scleral lenses are, however, associated with a variety of challenges that hinder their applicability in routine care settings.

Cyclosporine A 0.1%: Approved treatment in the European Union for DED patients with severe keratitis

Among the anti-inflammatory agents, cyclosporine A (CsA) is a potent immunomodulatory agent with anti-apoptotic properties relevant to managing DED.[5] A new formulation containing 0.1% (1 mg/mL) of CsA in an unpreserved oil-in-water cationic nanoemulsion (CsA CE; Ikervis®) has been approved in the European Union (EU) to treat severe keratitis in DED patients.[6] The once-daily therapeutic option is primarily indicated for the treatment of severe keratitis in adult patients with DED refractory to treatment with tear substitutes.[7] Ikervis® utilizes a nanoemulsion drug delivery system, Santen's Novasorb® technology, to effectively reduce ocular surface damage **(Figure 1)**.[8]

Figure 1. Novasorb® cationic nanoemulsion technology facilitates effective delivery of Ikervis®, permitting once-daily dosing.



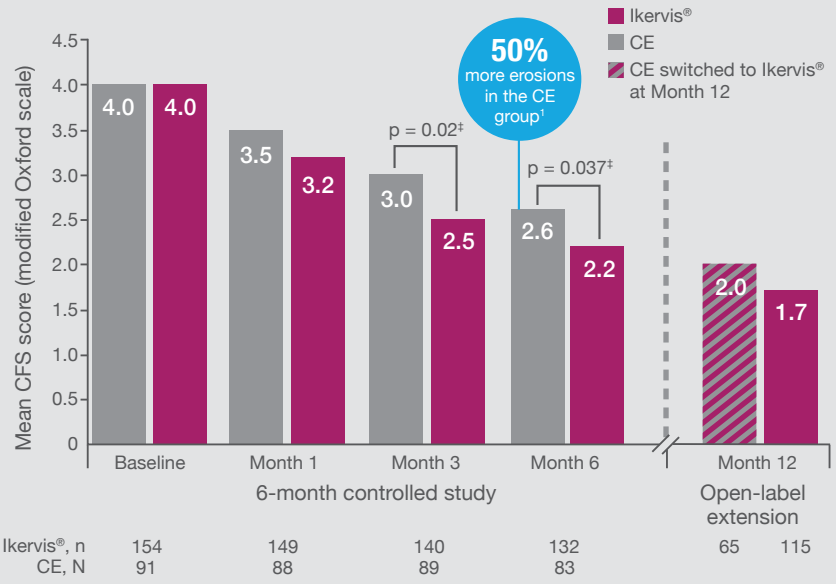
Recent attention has focused on the role of cyclosporine in the management of DED, and several clinical trials have evaluated the efficacy in a variety of clinical phenotypes of DED.[10,11] The preclinical and clinical testing of 0.1% CsA CE for the treatment of DED has demonstrated a positive benefit-risk ratio in this patient population.[11] The efficacy of 0.1% CsA CE eye drops was further evaluated in a pivotal phase III study (SANSIKA).[11]

The SANSIKA study

The SANSIKA study was a multicentre, randomized, double-blind, 2-parallel arm, 12-month trial that enrolled 246 DED patients with severe keratitis (defined as a corneal fluorescein staining [CFS] score of 4 on the modified Oxford scale). Analysis of the primary composite efficacy endpoint was performed, and results showed that patients achieving ≥2 grades improvement in CFS and a 30% improvement in symptoms (Ocular Surface Disease Index [OSDI] by month 6 was 28.6% with 0.1% CsA CE versus 23.1% with a vehicle, albeit statistically insignificant. Furthermore, assessment of corneal damage showed greater improvement with 0.1% CsA CE as compared to the vehicle in mean adjusted CFS change from baseline to month 6 (-1.764 vs -1.418, p=0.037) (Figure 2). Most importantly, the use of 0.1% CsA CE resulted in a significant reduction in human leukocyte antigen DR expression, a marker of ocular surface inflammation.[11]

On the planned secondary endpoint of CFS, patients who had received 0.1% CsA CE showed significantly less staining at months 3 and 6 than those who had received vehicle (p=0.024 vs p=0.037, respectively). The adjusted mean difference between the two groups in CFS was 0.35 at month 6.[11] This can also be interpreted as an average of 50% more punctate corneal lesions in the vehicle group compared with the intervention group.

Figure 2. SANSIKA: Ikervis® steadily decreased mean CFS scores over time

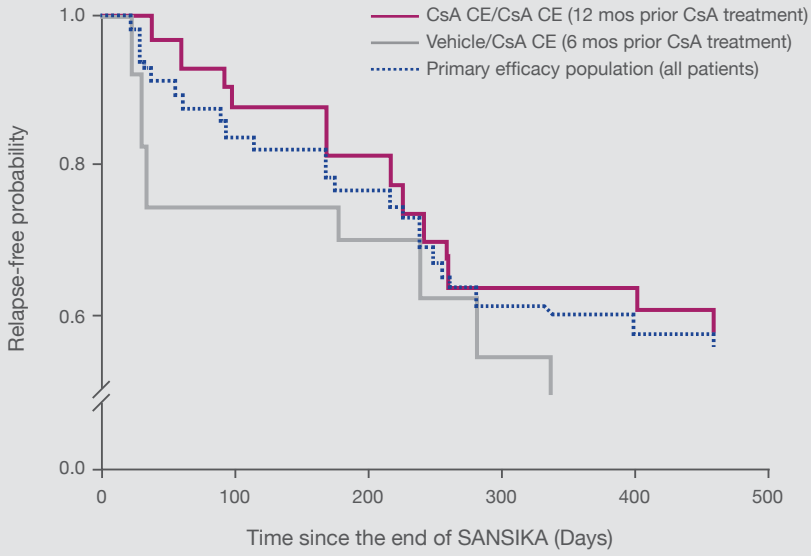


Adapted from Leonardi, et al 2016 and Van Setten, et al 2016.[11,12]

Post-SANSIKA study

A post-hoc analysis of the SANSIKA study was conducted to ascertain the relapse rates in patients who had previously received 0.1% CsA CE. Of the 62 markedly improved patients in the primary efficacy population, 61.3% did not experience a relapse based on CFS scores two years after the SANSIKA trial completion **(Figure 3)**.[7] Additionally, the time to relapse following 12 months of prior treatment with 0.1% CsA CE was ≤224 days.[7]

Figure 3. Post-SANSIKA: Relapse rates of dry eye disease patients with severe keratitis who have previously received Ikervis®[13]



Santen Pharmaceuticals. Data on File.

Real-world clinical practice on severe keratitis in Singapore

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An updated stepwise algorithm for the treatment of dry eye is the key difference between the initial TFOS DEWS and DEWS II reports. Based on the TFOS DEWS II treatment recommendations, cyclosporine is listed in Step 2 of the DED treatment algorithm, where topical, non-glucocorticoid immunomodulatory drugs are indicated.[1]

Treatment plan and outcomes (Patient case A)

Patient A is a 41-year-old female office worker who presented with significant symptoms of severe dry eyes. She complained of photosensitivity and ocular pain on computer use. The patient had no history of dry mouth or Sjögren's syndrome. She had bilateral laser-assisted in situ keratomileusis (LASIK) for high myopia and was on retinoic acid. The patient was referred by a general practitioner due to dry eyes that was unresponsive to lubricants.

On examination, patient's best-corrected visual acuity (BCVA) was 6/7.5 and 6/6 on the right and left eyes, respectively. OSDI was 59 (severe), with extensive punctate staining on both corneas, moderate conjunctival injection and mild lagophthalmos. She had reduced tear breakup time (TBUT; 3 seconds for both right and left eyes). Schirmer's test (with topical anaesthesia) result was 0 mm on the right and 1 mm on the left eye.

Initial plan

- Preservative-free topical lubricant (carboxymethyl cellulose and hyaluronic acid) and gel with temporary punctal plugs on both lower puncta
- 0.12% prednisolone
- Symptom recurrence

Revised plan

- Topical cyclosporine 1 mg/mL (Ikervis®) eye drops once daily

Treatment outcomes

- Good response to cyclosporine
- OSDI improvement of 34%
- Reduction in corneal punctate staining
- Improvement in Schirmer's test to 3 mm on the right and left eyes
- TBUT remained unchanged

Treatment plan and outcomes (Patient case B)

Patient B is a 63-year-old postmenopausal housewife who presented with significant symptoms of severe dry eye disease and Meibomian gland dysfunction (MGD). Symptoms reported were constant foreign body/gritty sensation, glare and intermittent blurry vision. There was no history of dry mouth or previous Sjögren's syndrome. She had bilateral cataract surgery in 2010 and is a heavy mobile phone and tablet user. She has tried over-the-counter lubricants recommended by a local ophthalmologist with no significant symptomatic relief.

On examination, patient's BCVA was 6/7.5 and 6/24 for the right and left eyes (monovision). Her OSDI was 45, with MGD in the lid margins of both eyes, moderate punctate staining on both corneas and mild conjunctival injection. She had reduced TBUT (3 seconds and 4 seconds for right and left eyes, respectively) and Schirmer's test (with topical anaesthesia) result was 4 mm and 3 mm on the right and left eyes, respectively.

Initial plan

- Regular preservative-free cationic emulsion, lubricant ointment and omega-3 oral supplements
- Intense pulse light therapy with permanent punctal plugs on both lower puncta
- Symptoms remained after 12 months

Revised plan

- Short course of 0.1% fluorometholone
- Topical cyclosporine 1 mg/mL eye drops once daily

Treatment outcomes

- Responded well to cyclosporine with OSDI improvement of 57%
- Notable improvement in clinical signs as shown by the clearance of corneal punctate staining
- Improved TBUT to 7 seconds and 8 seconds on right and left eye, respectively
- Marginal improvement in Schirmer's test to 4 mm in both eyes

Q&A

Q What is the difference in the side effect profile of the 0.05% versus the 0.1% formulation of cyclosporine in terms of irritation?

A Patients who are initiated directly on the 0.1% formulation do not seem to experience a high level of irritation. Cyclosporine 0.1% may be used either twice-a-day or four-times-a-day for paediatric cases of severe vernal conjunctivitis. Although children may complain of burning sensation, continuously using cyclosporine four-times-a-day is likely to result in improved outcomes. Good compliance has been reported and cyclosporine is generally well tolerated, even after several instillations in paediatric patients with vernal conjunctivitis.

Q What is your experience with using cyclosporine in patients with keratitis?

A Most eye drops will induce burning sensation in cases of severe keratitis. It could be useful to give doses over a short period and with steroids prior to the use of cyclosporine. This could lead to less burning sensation when cyclosporine is applied.

Recent recommendations have seen the introduction of cyclosporine A early in the disease course, including in cases of mild corneal staining, compared to previous guidelines. Furthermore, cyclosporine A can be used in cases of very severe keratitis and dry eye with stage 3 or 4 disease, as well as mild to moderate keratitis.

Q What is your opinion on patient compliance compared to previous formulations of cyclosporine in Asia?

A Compliance is always an issue for patients. In general, patients may complain of discomfort initially but over time they become adjusted to it as their eye condition improves and the drug becomes even more tolerable.

Q Is it better to administer the once-a-day instillation in the morning or at bedtime?

A The decision lies with the patient. They are usually reminded to use their eye drops at the same time they would do something else daily (eg, brushing their teeth or taking their hot chocolate before sleeping) to aid compliance. It is important that patients link their use of cyclosporine with something they do routinely and never forget – that helps with compliance.

Q What do you think about the use of cyclosporine in allergic diseases?

A Results from a 2016 study on the use of cyclosporine four-times-a-day in children with vernal conjunctivitis showed improved patient outcomes, in terms of signs, symptoms and quality of life. This could be the same in dry eye patients because their quality of life is very much impaired. In cases of vernal conjunctivitis, patients tend to improve psychologically once their symptoms improve. However, this does not seem to apply to paediatric cases due to their tendency to end therapy prematurely upon recognizing symptom improvement. DED is a chronic condition that requires long-term therapy. Abrupt treatment discontinuation would likely cause recurrent symptoms.

Practice Pearls

Three useful clinical tips to maximize patients' benefits from treatment with Ikervis®†:

- Steroid pretreatment with either topical 0.1% fluorometholone or 0.5% loteprednol 1–2 weeks should be considered before initiation of long-term 0.1% cyclosporine.
- Educate patients that cyclosporine drops are milky and can cause stinging, which can be minimized by instilling cyclosporine drops in the eye 5–10 minutes after administration of artificial tears.
- Set a 3-month target to evaluate progress as the beneficial effects of cyclosporine is generally observable after a few months.

† Ikervis® may not be approved and available in some countries. Please check with a local Santen office for more information on the local approved prescribing information.

References: 1. Craig JP, et al. *Ocul Surf* 2017;15:276-283. **2.** Stapleton F, et al. In: Dry Eye: A Practical Approach. Springer; 2015:21-29. **3.** Bron AJ, et al. *Cornea* 2003;22:640-650. **4.** Habay T, et al. *J Fr Ophtalmol* 2014;37:188-194. **5.** Jones L, et al. *Ocul Surf* 2017;15:575-628. **6.** Leonardi A, et al. *Ocul Immunol Inflamm* 2017;25:577-586. **7.** European Medicines Agency. Ikervis® - Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002066/WC500186590.pdf. Accessed on 1 November 2017. **8.** Lallemand F, et al. *J Drug Deliv* 2012;2012:604204. **9.** Doan S, et al. In: 8th International Conference on the Tear Film & Ocular Surface: Basic Science and Clinical Relevance; 2016:55. **10.** Stevenson D, et al. *Ophthalmology* 2000;107:967-974. **11.** Leonardi A, et al. *Eur J Ophthalmol* 2016;26:287-296. **12.** Van Setten GB, et al. *Invest Ophthalmol Vis Sci* 2016;57:2865. **13.** Santen Pharmaceuticals. Data on File; 2016.

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