Raising the Bar for Dry Eye Disease Therapy

Dear Colleagues,

Keratoconjunctivitis sicca (KCS), also known as dry eye disease (DED), is a multifactorial ocular surface disorder characterized by a loss of tear film homeostasis, inflammation, and ocular symptoms such as discomfort and visual disturbance.[1] The central mechanism of KCS is evaporative water loss, leading to hyperosmolar tissue damage. The process directly, or indirectly secondary to increased inflammation, causes a loss of epithelial and goblet cells, and precipitates decreased surface wettability and early tear film breakup.[2] This all serves to exacerbate hyperosmolarity via a "vicious circle."[2] In particular, chronic inflammation has been identified as a perpetuating factor in DED,[3,4] so controlling ocular surface inflammation has been found to help improve DED treatment outcomes.[5]

While short-term use of topical corticosteroids is reported to be a beneficial treatment for episodic worsening of DED symptoms and signs,[6] long-term use of topical steroids has clinical limitations due to potential side effects such as IOP elevation, infection, and cataract formation.[7] Conversely, the chronic use of cyclosporine A (CsA) to increase tear production has been found to be an effective and safe therapeutic strategy to manage many DED patients.[8,9] Researchers hypothesize that CsA's mechanism of action is related to immunomodulatory activity, which reduces local inflammation,[10] although the exact mechanism of action involved in enhancing tear production is not well understood.[11]

In 2003, the FDA approved a CsA emulsion with 0.5 mg/mL concentration, or 0.05% CsA, after it was found to be effective at treating moderate to severe dry eye disease in clinical trials.[11] However, treatment challenges have plagued the therapy due to cyclosporine's highly lipophilic nature and poor aqueous solubility.[10]

More than a decade later, dry eye therapy has taken another step forward since the FDA in 2018 approved CEQUA (cyclosporine ophthalmic solution 0.09%), a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca. Not only does CEQUA contain the highest FDA-approved concentration of CsA, it is the first and only approved CsA product incorporating a nanomicellar technology known as NCELL for improved delivery of cyclosporine and increased penetration to ocular tissues.

Nanomicelles, composed of polymers that encapsulate CsA molecules, exhibit a hydrophilic outer layer compatible with the aqueous environment of the tear film to facilitate transport through the tear film onto the ocular surface. In addition, their small size helps them gain entrance into corneal and conjunctival cells.[12,13] Once inside the tear film's aqueous layer,[10,13] the nanomicelles break up to release cyclosporine into the ocular tissues.[10,13] In a single-dose preclinical study, a CsA formulation using NCELL vs. a traditional CsA emulsion enabled nearly three times more of the molecule to penetrate the cornea and 1.6 times more to penetrate the conjunctiva.[12,14,15]

Along with positive findings for CEQUA's efficacy, clinical trials have shown CEQUA to exhibit a good safety and tolerability profile.[15-17] The most common adverse reactions following use of CEQUA have been instillation site pain (22%) and conjunctival hyperemia (6%),[18] with patients rating most ocular adverse events as mild (80%) or moderate (17%).[15]

It is clear that a new era has arrived for CsA, with the powerful combination of a higher concentration offered in conjunction with advanced drug delivery technology. This important clinical development is giving eye care practitioners another tool to help manage the chronic and inflammatory nature of DED for their patients.

–Scott E. Schachter, OD (Moderator)

Scott E. Schachter, OD (Moderator)
Ocular Surface Academy, Founder,
Pismo Beach, CA

Josh Johnston, OD, FAAO
Georgia Eye Partners,
Atlanta, GA

Alan G. Kabat, OD, FAAO
Salus University,
Elkins Park, PA

Bridgitte Shen Lee, OD, FAAO, FBCLA, FEAOO
Vision Optique,
Houston, TX

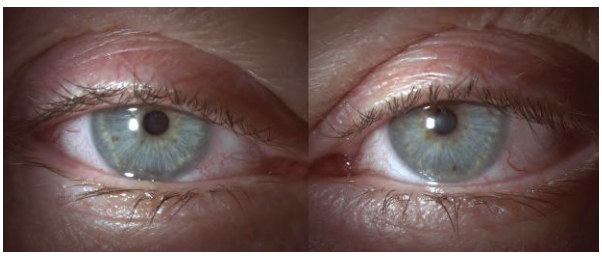
1 Dr. Schachter: Can you talk about what signs and symptoms today's keratoconjunctivitis sicca, or dry eye, patients are presenting with at the practice? How has this changed over the years?

Dr. Johnston: The classic signs and symptoms of dry eye are burning and stinging. The other complaints that are more prevalent now with increased patient and doctor awareness are fluctuating vision, decreased vision, pain, eye strain, and fatigue—even computer vision syndrome, these issues that are kind of relevant to dry eye these days. And there are many other masqueraders that can mimic dry eye. Clinical signs such as inflammation, hyperosmolarity, decreased tear breakup time, and corneal and conjunctival staining are vital diagnostic tools used today that have modernized how we evaluate this disease.

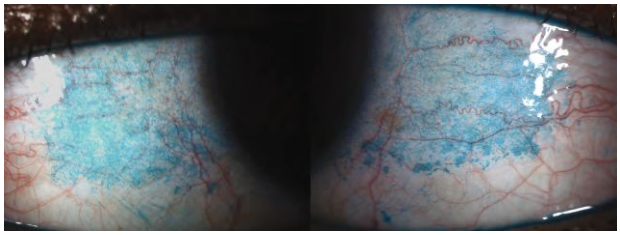
Dr. Kabat: I've been practicing for more than 30 years, and I've witnessed a substantial maturation in how we approach our patients with dry eye disease. In the past, we very naively waited for patients to tell us that their eyes felt "dry" or "irritated." We were not at all proactive in looking for dry eye, because we had few solutions that could truly help. In fact, dry eye was considered little more than a nuisance by many eye care practitioners.

Today, we recognize that many of the early clues to ocular surface disease are subtle and vague. Sometimes, the patient reports little more than blurry vision, or glare, or difficulty with prolonged visual tasking such as reading, driving, or viewing a computer screen. We recognize that these visual changes are, in many cases, the first indications of tear film instability.

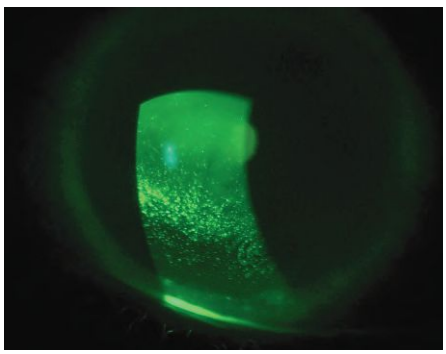
And as tear instability becomes more chronic, hyperosmolarity and inflammation become manifest. It is at this point that we then begin to hear complaints about discomfort, such as burning, stinging, and foreign body sensation. In my clinic, I like to quantify patients' complaints by using a validated symptom questionnaire, such as the Ocular Surface Disease Index (OSDI). This tool may have little predictive value as to the severity of dry eye signs, but it does help to establish the degree to which the patient's activities of daily living are adversely impacted by the disease.



Dry Eye Disease Presentation. Dry eye disease often presents with vague symptoms and red, irritated-looking eyes. Careful examination with vital dyes will reveal ocular surface damage. ***Photos: Alan G. Kabat, OD, FAAO***



Vital Dye Staining. Lissamine green shows devitalized areas of the conjunctiva (and cornea) that lack adequate mucin protection. This photo shows significant staining of the right and left temporal bulbar conjunctivae.



Coarse Staining. Disease progression leads to corneal epithelial breakdown, as demonstrated by coarse staining with sodium fluorescein. Patients like this are usually prime candidates for anti-inflammatory therapy.

In terms of dry eye signs, we have always relied on slit lamp examination using vital dye staining of the cornea and conjunctiva, as well as tear film break up time to establish a diagnosis.

We may have even used some very time-consuming and uncomfortable methods such as the Schirmer test in order to estimate tear volume and production. Fortunately, today, much of the diagnostic testing can be performed with semi-automated technology to determine tear meniscus height, noninvasive tear break up time, and even lipid layer thickness. Moreover, point-of-care testing can give us an indication as to whether the inflammatory cascade has been initiated, in terms of hyperosmolarity or the presence of matrix metalloproteinase-9 in the tear film. These advances in dry eye evaluation allow us to diagnose and intervene sooner than in the past, averting more serious presentations and complications.

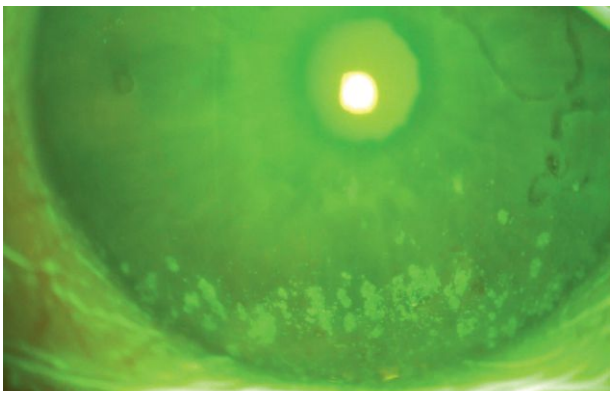
Dr. Shen Lee: My private practice provides both comprehensive primary eye care and medical services, which include dry eye disease, specialty contact lenses, and myopia management. We screen for dry eye symptoms during the case history and the preliminary testing. In addition, we inquire about our patients' digital device usage and habits, and any digital eye strain symptoms that include dry eyes.

During the slit lamp exam after the Goldmann tonometry, I can usually see the clinical signs of blepharitis, *Demodex* manifestations, conjunctiva follicular or papillary response, cornea staining, and tear film quality. The findings are discussed with patients, especially if they match the presenting symptoms. Patients who show significant clinical signs or have reported symptoms are invited to return for a separate comprehensive ocular surface disease (OSD) exam.

In 2016, we started taking meibomian gland images of

every patient age 18 and older, and every symptomatic patient younger than age 18. Our discovery of the high prevalence of meibomian gland dysfunction (MGD) among the healthy patient population (young and old) has changed how we practice. In addition, a discussion of dry eye symptoms is now included with every patient's comprehensive annual eye exam.

Dr. Schachter: We can stereotype the typical dry eye sufferer as a post-menopausal woman, but we are now seeing dry eye disease in all demographics. Younger patients are on ADD/ADHD and allergy medications as well as oral contraceptives, which may dry out their eyes. This is at the same time digital device use is at an all-time high. We give all patients a validated questionnaire to elicit symptoms, and are finding that screen time is up, and symptoms are as well.



Inferior Corneal Staining. Inferior corneal staining with fluorescein seen with Wratten #12 filter. This 70-year old female patient had a diagnosis of keratoconjunctivitis sicca. *Photo: Scott E. Schachter, OD*

2 Dr. Schachter: How has your dry eye management approach changed over recent years, and what have been your greatest challenges in developing a successful treatment regimen?

Dr. Johnston: Initially in my career–I graduated in 2004–I ignored dry eye. I thought it was boring, it was unimportant. I would hand patients many different kinds of artificial tears and say, 'Come back in a year and see me.' In 2009-2010, I adopted the model of staining every patient, looking for signs and symptoms, talking to patients about their symptoms, and looking closely for this disease state. At that point, I really became aggressive about diagnosing and treating inflammation. Inflammation, we now know, is the root cause of aqueous deficient dry eye, and we can use things like corticosteroids short-term. But those have side effects, and they're off-label. So we need something to address inflammation long-term that's safe and that helps the body produce more natural tears. That was sort of step 1. Step 2, we know there's more information out there about meibomian gland dysfunction and obstruction. Dry eye is multifactorial; it's not easy, it's complex. There's a lot going on, and you need to examine the biofilm of the lids, assess for issues such as lagophthalmos, micro-lagophthalmos, and conjunctivochalasis while also evaluating staining, meibomian gland function for the quantity and quality of the meibum–looking for things like inflammation, hyperosmolarity, and decreased tear breakup time. All of these different factors are relevant. So now that I'm doing this at a high level, I've learned that dry eye diagnosis and treatment can be very esoteric. It's gone from basic treatments using an assortment of tears, to targeting inflammation, to evaluating and managing the entire lacrimal functional unit with a wide variety of therapy options available today.

Dr. Kabat: Until the late 1990s, drug therapy for dry eye was unheard of. We had artificial tears, which accounted for as much as 80% of our therapeutic management, and the remainder of patients became candidates for punctal occlusion. Dr. Steven Pflugfelder and other pioneers showed us that anti-inflammatory medications could provide significant relief for those suffering from dry eye,[19] but many of us hesitated because the approach involved off-label use of a corticosteroid–a drug class that we had been taught was to only be used in extreme cases and with the utmost caution. When topical cyclosporine was introduced in 2003, we were initially elated to finally have a medication that was specifically indicated for treating keratoconjunctivitis sicca. However, we quickly found that a good percentage of patients failed to respond to this new formulation in the manner that we had hoped. Moreover, it was very difficult to predict which patients would succeed and which would ultimately fail or discontinue therapy because of intolerability, cost issues, or simply frustration.

My biggest challenge in developing an effective treatment regimen for dry eye is two-fold. First, it has taken many years to realize that not all dry eye is alike in its composition or manifestations, and, hence, there is no single therapy that works for every patient. A good dry eye doctor understands that, to be successful, one must first identify the most significant contributory element of the ocular surface disease and manage it aggressively through whatever means are most appropriate. Second, when inflammation is present, we can no longer afford to use agents that take up to six months to begin yielding improvement. If my experience has taught me anything, it's that patients are not very patient! The symptomatic individuals who I see today want and expect relief, or at least some indication of recovery, in a matter of days or perhaps weeks. If I'm lucky, they may give me one or two months.

Dr. Shen Lee: My dry eye management approach has changed from taking care of symptomatic patients to also addressing concerning clinical signs demonstrated by patients before they become problematic. The improvement in diagnostic technology (meibomian gland imaging and osmolarity testing), two new prescription eye drops, and noninvasive treatment options (meibomian gland expression, microblepharoexfoliation, intense pulsed light) have made major improvements in how we take care of dry eye patients.

The greatest challenge is the general lack of public understanding about dry eye disease. The majority of patients have not heard of meibomian gland dysfunction, and they do not understand why their health insurance will not cover all of the effective treatments.

Dr. Schachter: Years ago, I felt like many of my colleagues do—that treating dry eye disease just wasn't important enough. Once I recognized the impact of dry eye on my patients' vision, I embraced the expert recommendations of the TFOS Dry Eye Workshop of 2007 and introduced a process into practice for managing the disease. That took some fine-tuning, but it didn't take long before it was part of every eye exam.

3 Dr. Schachter: How did the initial approval of cyclosporine A (CsA) in 2003 change the dry eye treatment landscape, from your perspective?

Dr. Johnston: I think it was huge. It was the first FDA-approved drug to treat dry eye due to ocular inflammation. By treating and addressing inflammation—the root cause of aqueous deficient type—we were able to decrease inflammation and help the body produce more natural tears. With that FDA approval, we saw more understanding among our colleagues—ophthalmologists and optometrists alike—about this disease state and treating inflammation. We also saw an uptick in consumer awareness about dry eye through direct-to-consumer marketing leading to increased education and exposure, increased prescriptions, and basically a landmark drug that brought this drug category to where it is today.

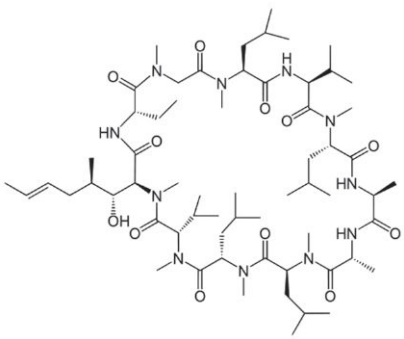
Dr. Kabat: After the release of CsA 0.05% in 2003, even doctors who had previously taken little interest in managing dry eye became prescribers overnight because there were virtually no safety issues with the medication and the message was very clear: Dry eye is inflammatory, and CsA is a potent immunomodulatory agent. Unfortunately, as with so many newly introduced therapies, the product simply did not live up to the hype. Many patients were unwilling to continue using a therapy that afforded them little tangible benefit over the course of the first three months, and so they either discontinued therapy independently or complained to the doctor such that he or she would move on to another therapy—usually punctal plugs.

Dr. Shen Lee: It was very exciting to finally have a prescription eye drop to treat dry eye disease. Patients were happy to have a pharmaceutical option in addition to over-the-counter tear supplements.

Dr. Schachter: The introduction of Cyclosporin A finally gave us an option other than artificial tears. When I started following the TFOS DEWS treatment algorithm and prescribing CsA, patients started getting meaningful symptomatic relief, and objective signs also improved.

4 Dr. Schachter: Can you talk about treatment obstacles with the earlier formulations of CsA in your patients? How did this impact your ability to manage patients?

Dr. Johnston: We know cyclosporine is a great molecule; it's efficacious, it's been around for 17 years now to treat ocular inflammation, commercially approved. I didn't see a lot of obstacles with CsA, but in some cases, all three FDA-approved treatments might take a while for patients to get a symptomatic breakthrough. We know CsA works, even pretty quickly in some patients, but it's all about symptoms. So, if patients aren't getting that symptomatic breakthrough and feeling better, that's one obstacle. With this disease state in general, patients—especially those with more severe cases—can feel like the response to treatment can be slow.



Cyclosporine Molecule. Ciclosporin was isolated in 1971 from the fungus Tolypocladium inflatum and came into medical use in 1983.[20] It is on the World Health Organization's List of Essential Medicines as one of the safest and most effective medicines needed in a health system.[21]

Dr. Kabat: Between the side effects—most notably the stinging on instillation—and the lengthy delay in achieving any substantial clinical improvement in signs or symptoms, a lot of patients simply quit using their drops. I'm sure many blamed their doctors and moved on to other practices. It was very humbling and very, very frustrating.

Dr. Shen Lee: During the early 2000s, we did not have sophisticated diagnostic tests or the ability to analyze and view meibomian glands. For patients with more severe corneal staining and very low tear quality, we used prescription steroid drops on a tapered schedule in conjunction with the first-generation 0.05% CsA drops. It was very important to teach patients to stay on CsA even if they did not notice more immediate symptom relief, and to stay on the prescribed course even after feeling better.

Dr. Schachter: Some of my patients struggled with CsA over the years because of how long it took them to experience symptomatic improvement. Many discontinued use or identified themselves as CsA failures. However, they didn't take the medication long enough to really know what their outcome could have been. Historically, CsA required thorough patient

education to set up appropriate and realistic expectations.

5 Dr. Schachter: How did the 2018 approval of CEQUA with a higher concentration, and NCELL technology to improve cyclosporine delivery and increase penetration to ocular tissues impact your management of dry eye patients?

Dr. Johnston: Doctors love innovation, patients love innovation. So it's nice to see new formulations and FDA approval of advancing therapeutics. The thought here with the higher concentration and the nanomicelles is you get increased uptake into the ocular tissues, which then leads to higher bioavailability with potentially increased speed of the mechanism of action addressing inflammation. With a higher concentration of cyclosporine, as well as the nanomicelles technology, or NCELL technology, the data is compelling showing an increased uptake of this into the ocular tissues, whether that be the corneal tissue or the conjunctival tissue in one study. If we can deliver a medication at a higher dose, at a higher concentration, increasing the active drug with greater bioavailability, ultimately we have a therapeutic that might work quicker in some patients.

Dr. Kabat: Fortunately, several companies continued to work on topical dry eye formulations to provide an alternative to CsA 0.05%. We saw the first of these formulations launch in 2016, and it really renewed my faith in the dry eye cause. Here were patients who were just barely getting by with artificial tears and/or CsA 0.05%, and within a month of starting this new medication, they were experiencing unparalleled relief. Similarly, when CEQUA gained approval and was finally made available to us in 2019, we witnessed that same type of watershed moment. In patients returning for three- or four-week follow-up visits, we were already seeing substantial improvements in ocular staining and visual function. I absolutely believe that the higher concentration of CsA in CEQUA, combined with NCELL technology to help ensure greater bioavailability in the target tissues is the reason for this success.

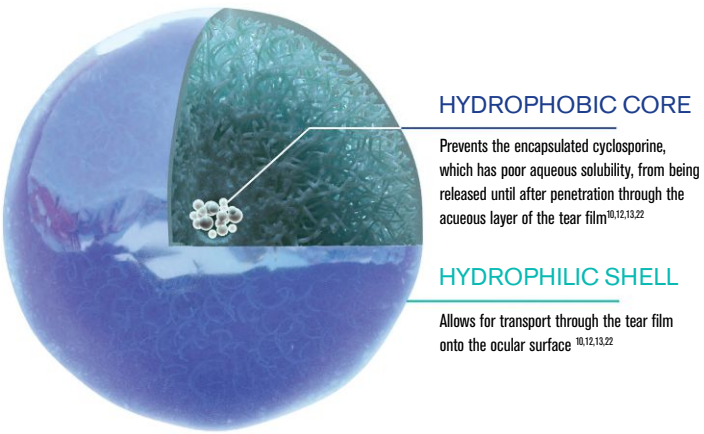
In a single-dose preclinical study, a CsA formulation using NCELL vs. a traditional CsA emulsion enabled...

Up to 3X higher absorption across ocular tissues.[12,14,15]

Dr. Shen Lee: The faster onset of conjunctiva and corneal staining improvement or clearing has helped patients feel better sooner and has increased patient compliance with staying on the treatment course.

Dr. Schachter: CEQUA caused me to look at CsA through a new lens. The improved penetration and higher concentration of CsA provided my patients with another effective tool in treating dry eye disease. The more options, the better for both patient and provider.

NCELL™ TECHNOLOGY ENHANCES OCULAR DELIVERY OF CYCLOSPORINE[12,15]



CEQUA is the first and only FDA-approved treatment to combine cyclosporine with NCELL technology for improved delivery of cyclosporine and increased penetration to ocular tissues.[12,15,17] NCELL uses nanomicelles composed of polymers–a blend of polymers including polyoxyethylene hydrogenated castor oil 40, or HCO-40, and Octoxynol-40, or Oc-40–that encapsulate cyclosporine molecules.[12,13]

The units of polymers self-assemble into a nanoscale aggregate via a thermodynamic process. Once assembled, the polymers work together as a unit, or nanomicelle, with a hydrophilic outer layer and hydrophobic core. The hydrophilic outer layer, which is compatible with the aqueous environment of the tear film, allows for transport through the tear film onto the ocular surface. At the same time, the hydrophobic core prevents the encapsulated cyclosporine from being released until after the nanomicelle penetrates the aqueous layer of the tear film.

The small size of the nanomicelles, which measure an average of 22 nanometers or approximately one three-thousandth the width of a human hair, helps facilitate the entry of cyclosporine into corneal and conjunctival cells. The nanomicelles penetrate the aqueous layer of the tear film and release the active cyclosporine molecules for penetration into ocular tissues.

Once released, cyclosporine starts working to reduce inflammation, helping improve the ocular surface and increase tear production.

6 Dr. Schachter: What differences did you notice in patients treated with this newer formulation of CsA vs. earlier formulations?

Dr. Johnston: It's still pretty early, but, anecdotally, we've seen some patients respond faster on this new formulation. Dry eye is a tough disease state; there's no magic bullet or cure. A lot of the patients I see are more advanced, older in age, and have a lot going on as far as risk factors. So dry eye is particularly challenging in the patient population that I serve. But I think patients are excited about new options–whether that be a different formulation or new technology like the NCELL technology. And the thought here, and we see this echoed in the clinical data, is that this new formulation has the potential to work faster.

Dr. Kabat: More than anything else, I noticed patient acceptance. When I ask, "How are you doing with these drops?" a lot fewer patients tell me, "I'm not sure." More often I hear things along the lines of "I like them!" and "I'm seeing better" and even "I don't have to use my artificial tears as often anymore." It's very encouraging, and it makes my next move just that much easier.

Dr. Shen Lee: I have seen complete central cornea staining clearing in some of my long-term dry eye patients. The clinical data shows that 65% of patients on 0.09% CsA achieved complete central cornea clearing on day 84.[16]

Dr. Schachter: CEQUA, with an increased concentration of CsA and novel vehicle, provides the symptomatic improvement patients are seeking. At the six-week follow up, many identify a decrease in symptoms and improved comfort.

CEQUA provides the **HIGHEST FDA-APPROVED CONCENTRATION** of cyclosporine (0.09%)[10,17]

7 Dr. Schachter: Following the use of CEQUA, the most common adverse reactions, which were reportedly primarily mild (80%) or moderate (17%), were instillation site pain (22%) and conjunctival hyperemia (6%). What has your experience been with adverse events in patients?

Dr. Johnston: My experience using CEQUA has been great. The tolerability is wonderful. When we look at therapeutics, we want drugs that are effective and efficacious, and we want them to be well-tolerated by patients, with low AEs, and obviously commercially available and easy to get, from an access and affordability standpoint. So this is a medication that I am never concerned about with tolerability. We see some patients who complain about burning or stinging, or instillation site pain sometimes, but it's very mild. Most patients have no pain with use. So it's never been a barrier to me to prescribe this. I think most of my patients are doing pretty well with it.

Dr. Kabat: I may be the odd-man-out here, but I like to try all the new topical formulations that hit the market whenever feasible, just so that I can relate to patients' complaints. When I first put CEQUA in my eye, I had no adverse reaction whatsoever–no stinging, no blurring of my vision, no unusual taste after five or ten minutes. Truly, there were no adverse effects whatsoever. Now, I will admit that some of my patients (and my colleagues) have reported some stinging with continued use, but on the whole, it is typically mild and quite tolerable. As a long-time practitioner, I understand that many excellent drugs can cause irritation upon instillation. Most of our glaucoma drugs induce temporary stinging and redness of the eyes, but we ask our patients to persevere because in the end, the treatment is necessary and the adverse events are fleeting. Our approach should be no different with dry eye therapies like CEQUA.

Dr. Shen Lee: The instillation site burning sensation is more common in patients with worse clinical presentations, especially those patients with high superficial punctate keratitis (SPK) staining scores. I use the following two methods to educate patients and to help alleviate instillation discomfort symptoms:

1. I put sample CEQUA drops in the patient's eyes after the dry eye exam to both assess the patient's sensitivity and educate the patient that the "burning" sensation is normal. I tell patients that the burning sensation reduces with each week's use, and I make sure they understand to wait 15 to 20 minutes before they put on their contact lens.
2. For patients who have a high SPK staining score and who experience instillation burning sensation, I ask them to use a preservative-free tear first thing in the morning, wait 10 minutes, and then put in CEQUA.

It is important to educate patients about potential symptoms and to help them figure out a morning/evening routine with their eyecare and skin care products. We email every dry eye patient a very detailed step-by-step plan for using their drops (OTC and Rx), lid/lash hygiene products, and other dry eye at-home care products.

Dr. Schachter: In my clinical experience, the adverse events experienced have been mild. As always, when prescribing a new medication, it's important to let patients know what side effects they may experience. We do this by instilling a drop in one eye the same day we prescribe it. Typically, when patients know what side effects they may encounter, it helps them maintain compliance if those effects are mild.

8 Dr. Schachter: In what clinical cases/scenarios, do you feel CEQUA performs best for your patients?

Dr. Johnston: I think CEQUA works best when you catch dry eye patients early. For example, if you have a 35- or 40-year-old patient suffering from dry eye, these patients respond much quicker than say an 85-year-old female with Sjogren's and rheumatoid arthritis, who has had multiple ocular surgeries. If you start to stack on increased age and other risk factors, it just takes much longer to get an effective decrease in clinical signs as well as improvement in symptoms. So I think CEQUA works well when you catch dry eye early on in your patients–before they're further down that severity pathway.

Dr. Kabat: Based upon the clinical studies and personal experience, I believe CEQUA is currently the best initial choice for those patients who have documented inflammatory dry eye disease with symptoms that are exceeded by clinical signs, particularly epithelial disruption of the cornea and/or conjunctiva as demonstrated by fluorescein and lissamine green, respectively. I also feel it is a good option for patients who had had some success with CsA 0.05%, but who now find that they need to use it more frequently, for example three to four times a day, to obtain the same relief that they previously had with BID dosing. And while it may seem counterintuitive, I have even had a few successful cases where patients have been switched to CEQUA after experiencing unacceptable side effects or a poor response to lifitegrast 5%. Despite being completely different drug classes and having different mechanisms of action, both ultimately address inflammation at the level of the ocular surface, and, hence, one may be able to "fill the void" where the other cannot.

Dr. Shen Lee: Unfortunately, in the US, the patient's health insurance coverage dictates what prescription eye drops can be used. That said, we know that CEQUA has a broad and effective coverage for patients who are diagnosed with dry eye disease.

OFFICE TIPS FOR PATIENT SUCCESS WITH CEQUA.

Dr. Shen Lee: It is important to train a designated team member to learn the prior authorization (PA) process and to help patients obtain insurance coverage for CEQUA to increase prescription fill rates. In addition, a detailed treatment plan helps patients improve their understanding of and compliance with the doctor's recommendations

Dr. Schachter: Many of my patients have tried other medications without success. Those failures may have been due to adverse events or lack of efficacy for those particular individuals. They are often concerned that there are no options for them and are excited to try CEQUA.

9 Dr. Schachter: What do you say to critics of older CsA formulations who complain about a lack of efficacy or effect in their patients, with respect to a newer offering that includes a higher concentration and improved drug delivery platform?

Dr. Johnston: When we look at the older formulation, it's a billion-dollar-a-year drug,[23] so that's pretty robust validation that it's working. However, we get some doctors and patients who say that the drug does not work as well as they want. But again, it's all about symptoms. So, we have to talk to our doctors and patients and ask them how they are using the medication. I often hear, "Oh, I used it for two weeks." Well, two weeks is not enough. This is a chronic disease state. It's progressive. You need therapeutics to be onboard sometimes for a lifetime. The patient may not respond in two or even four weeks, depending on how severe they are. Now, it's nice to have new therapeutics that are available with higher concentrations and different delivery technology with the hope of increasing delivery to the ocular tissue to speed things up and give these patients a better chance at improving signs and symptoms of dry eye.

Dr. Kabat: My biggest criticism of 0.05% CsA emulsion has always been that it cannot afford patients the improvement they desire within the time frame that they are willing to invest in therapy. If we're being honest, we now live in a world that expects, and even demands, immediate gratification. Those colleagues who fail to recognize the distinctive qualities of CEQUA are clearly not aware of the benefits that enhanced drug delivery systems bring to the game. CEQUA with NCELL technology is just the latest in a long line of well-established ophthalmic drugs being repurposed using new delivery models in order to achieve greater efficacy, tolerability, and safety. Before the year is over, I predict that we will see several more new products in the United States that employ existing medications in unique ways to achieve substantially improved outcomes for dry eye patients.

Dr. Shen Lee: So much technology improvement has happened over the last 15 years. Eye care professionals need to learn the "3 Cs of CEQUA" and prescribe this new formulation to their dry eye patients. They are:

1. **Concentration:** The CsA concentration increased from 0.05% to 0.09%.
2. **Composition:** CEQUA is encapsulated inside a high-tech nanomicelles polymer.

CYCLOSPORINE HELPS RESTORE TEAR PRODUCTION[17]

Although the exact mechanism of action of cyclosporine is not known, cyclosporine has helped restore tear production in patients with ocular inflammation due to dry eye by acting as a partial immunomodulator. Since poor aqueous solubility has limited cyclosporine's ocular tissue penetration, CEQUA's nanomicelles are designed to enhance the ocular tissue penetration.[10,12,13]

- **Nano** means the size of each molecule is 22nm, which is 1/3000th the width of a single human hair.
- **Micelles** have a hydrophilic exterior that facilitates transport through the aqueous tear, and a hydrophobic core that keeps the CsA molecule stable until it reaches the ocular surface.

3. **Cornea Clearing**
   - Decrease in cornea staining can be achieved in **1 month** after using CEQUA.
   - Complete central cornea clearing can be achieved in **65% of patients after 3 months** on CEQUA.

Dr. Schachter: When I educate my patients about CEQUA, I highlight the differences between prior formulations and lean on CEQUA's own data to support my discussions. Many of my patients have done their homework and want to have a greater understanding of what I'm prescribing and why it will benefit them.

PHARMACOKINETICS OF CYCLOSPORINE DELIVERED WITH NCELL[14]

Here is a snapshot of the study, published in the Sept. 9, 2019, online edition of the *Journal of Ocular Pharmacology and Therapeutics* evaluating the preclinical pharmacokinetics of cyclosporine delivered with NCELL technology and the resulting positive findings for the new delivery model:

Researchers evaluated the ocular distribution, tolerability, and systemic exposure of cyclosporine (CsA) in New Zealand white rabbits following topical administration of OTX-101, a novel, clear aqueous nanomicellar solution developed for the treatment of dry eye disease (DED).

The study design included single- and repeat-dose phases. In the single-dose phase, rabbits received a single instillation of OTX-101 0.05% or CsA ophthalmic emulsion 0.05% (Restasis®, Allergan) as a comparator. In the repeat-dosing phase, OTX-101 (0.01%, 0.05%, or 0.1% CsA) or comparator was instilled 4 times per day for 7 days. Samples collected included whole blood, tears, and ocular tissues/fluids (aqueous humor, choroid-retina, conjunctiva, cornea, superior eyelid, third eyelid, iris/ciliary body, lacrimal gland, lens, sclera, and vitreous humor). CsA concentrations were analyzed using liquid chromatography-tandem mass spectrometry.

Analysis included samples from 112 rabbits. The highest concentration of CsA following a single OTX-101 0.05% instillation occurred in the third eyelid (Cmax=1,200 ng/g). Concentrations of CsA in the cornea and superior bulbar conjunctiva increased in a dose-related manner following repeated administration of OTX-101 formulations; Cmax [Tmax (h)] for cornea was 1,543 ng/g (6.50), 5,410 ng/g (7.0), and 8,123 ng/g (6.50), for 0.01%, 0.05%, and 0.1% CsA concentrations, respectively; for superior bulbar conjunctiva was 726 ng/g (6.50), 1,468 ng/g (6.50), and 2,080 ng/g (6.25), respectively.

Researchers concluded that OTX-101 topical ophthalmic instillation resulted in extensive distribution of CsA in ocular tissues, particularly in target tissues for DED (cornea and conjunctiva), while systemic exposure was negligible.

10 Dr. Schachter: Do you have any case examples you could share about how CEQUA has helped specific DED patients in your practice increase their tear production and better manage their disease?

Dr. Johnston: Most patients have a combination of aqueous deficient as well as evaporative dry eye, so what are you going to do for that? Some of these treatments are out of pocket, and the patient might still be dry. So we need to prescribe a therapeutic that will decrease inflammation and help the body to produce more natural tears to help improve symptoms. Hundreds of our patients have used therapeutics like CEQUA and noticed an improvement in symptoms. Ultimately, the drug is increasing tear production and decreasing inflammation. It's been fun to have another option out there, and a lot of our patients, if we correctly diagnose them and catch them early, will do well on this therapy.

Dr. Kabat: Unfortunately, COVID-19 really interfered with our ability to follow-up and gain feedback from the numerous patients we initiated on CEQUA in the early part of this year. Only a dozen or so of my patients who were seen and started on CEQUA were able to return for multiple follow-ups. But of those, I recall that the improvement in corneal staining was the most remarkable aspect of their change. I had few, if any, tolerability issues, and while access is always a bit challenging with newly approved drugs, we found ways to get the drug to more than 90% of the patients who needed it and wanted it. I cannot recall more than one or two patients who have found the adverse effects to be intolerable. I think the most encouraging thing was watching patients who were simply ready to give up using their CsA 0.05% because it "wasn't doing any good," come "back from the brink" within three to four weeks on CEQUA BID. That's a very rewarding feeling for any health care provider. ◆

1. Craig JP, Nichols KK , Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017 Jul;15(3):276-83.
2. Bron AJ, de Paiva CS 2, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. Ocul Surf. 2017 Jul;15(3):438-510.
3. Jerkins GW, Pattar GR, Kannarr SR, et al. A review of topical cyclosporine a formulations–a disease-modifying agent for keratoconjunctivitis sicca. Clin Ophthalmol. 2020; 14: 481-9.
4. Rolando M, Barabino S, Mingari C, et al. Distribution of conjunctival HLA-DR expression and the pathogenesis of damage in early dry eyes. Cornea. 2005;24(8):951-4.
5. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. Ocul Surf. 2017;15(3):575-628.
6. Yang C-q, Sun W, Gu Y-s. A clinical study of the efficacy of topical corticosteroids on dry eye. J Zhejiang Univ Sci B. 2006; Aug;7(8):675-8.
7. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. Eye 2006;20:407–16.7.
8. Labetoulle M, Leonardi A, Amrane M, et al. Persistence of efficacy of 0.1% cyclosporin a cationic emulsion in subjects with severe keratitis due to dry eye disease: a nonrandomized, open-label extension of the SANSIKA study. Clin Ther. 2018 Nov;40(11):1894-1906.
9. de Oliveira RC, Wilson SE. Practical guidance for the use of cyclosporine ophthalmic solutions in the management of dry eye disease. Clin Ophthalmol. 2019;13: 1115-22.
10. Cholkar K, Gilger BC, Mitra AK. Topical, aqueous, clear cyclosporine formulation design for anterior and posterior ocular delivery. Transl Vis Sci Technol. 2015;4(3):1-16.
11. Highlights of Prescribing Information: RESTASIS® Available at: https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/RESTASIS_pi.pdf
12. US Patent 9,937,225 B2.
13. Mandal A, Bisht R, Rupenthal ID, et al. Polymeric micelles for ocular drug delivery: from structural frameworks to recent preclinical studies. J Control Release. 2017;248:96-116.
14. Weiss SL, Kramer WG. Ocular Distribution of Cyclosporine Following Topical Administration of OTX-101 in New Zealand White Rabbits. J Ocul Pharmacol Ther. 2019 Sep;35(7):395-402.
15. Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.
16. Tauber J, Schechter BA, Bacharach J, et al. A phase II/III, randomized, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of otx-101 in the treatment of dry eye disease. Clin Ophthalmol. 2018 Oct 2;12:1921-9.
17. CEQUA [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2018.
18. Highlights of Prescribing Information: CEQUA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210913s000lbl.pdf
19. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren syndrome. Ophthalmology. 1999 Apr;106(4):811-6.
20. Watts R, Clunie G, Hall F, et al. Rheumatology. New York: Oxford University Press; 2009.p. 558.
21. World Health Organization. World Health Organization model list of essential medicines: 21st list 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?sequence=1&isAllowed=y (last accessed July 30, 2020).
22. Cholkar K, Patel A, Vadlapudi AD, et al. Novel nanomicellar formulation approaches for anterior and posterior segment ocular drug delivery. Recent Pat Nanomed. 2012;2(2):82-95.
23. Allergan reports fourth quarter and full-year 2019 financial results. Bloomberg. 2020; Feb 10. Available at: https://www.bloomberg.com/press-releases/2020-02-10/allergan-reports-fourth-quarter-and-full-year-2019-financial-results (last accessed July 23, 2020).