Nonpharmaceutical Therapies for Dry Eye Disease

Milton M. Hom, OD, FAAO

The complex pathophysiology of dry eye disease lends itself to an equally multifaceted therapeutic approach—including, in recent years, physical or nonpharmaceutical corrective measures.

Dry eye disease (DED) affects millions in the US and throughout the world. Its incidence is increasing as many of us spend increasing time using handheld digital devices. Staring at a lit screen on a digital device—ie, smartphones, electronic tablets, or computers—prolongs the interblink interval and increases the proportion of incomplete blinks and frequency, which promote tear evaporation, inflammation, and, eventually, meibomian gland dysfunction (MGD).1

While still thought to be a disease related to increasing age, an increasing proportion of young people are suffering from DED, which is very possibly related to frequent and chronic use of cell phones and digital devices in all age groups, but disproportionately among the young. Recent studies have shown that people younger than 40 to 45 years of age check their phones more frequently and spend more total time per day in front of digital devices compared with individuals older than 40 to 45 years.2,3 It is important to note that most oft-cited epidemiological studies correlating DED with aging predate the introduction of the iPhone in 2007 and the commonality of tablets and laptop computers.4 Research is needed to better understand the effects of ocular surface stressors such as digital device use in younger patients.5 In my practice, however, evidence abounds; it is no longer uncommon for patients in their twenties—both women and men—to complain of ocular surface symptoms and have markedly abnormal meibography (Figure 1).

Changing demographics hold significant implications for how DED is treated now and will be in the future. In my opinion, therapies are needed that appeal to the full range of age groups and lifestyles. This includes younger patients, many of whom are reluctant to use pharmaceuticals, preferring “organic” and “natural” remedies. There is also poor acceptance of daily eye drops among patients with arthritis or other disabilities that make them hard to instill. Further, some patients feel burdened by eyedrops or forget to use them regularly. Effective alternatives to pharmaceuticals and drop-based therapies are well suited for these populations.

Drug companies are looking toward long-term drug delivery systems and nonpharmaceutical interventions to meet the needs of chronic disease patients and avoid encroachment by generic substitution. Innovations such as minimally invasive glaucoma surgery (MIGS) and drug depot implants eliminate or reduce dependence on daily drops and are rapidly changing the

FIGURE 1 Abnormal meibography of male in his 20s. A. Lower lid shows shortened glands. B. Upper lid has tortuosity. (Courtesy of Dr. Hom)
face of glaucoma treatment. Similarly advances in DED management—including “alternative” or drug-free modalities—may prove useful to clinicians and patients.

**Current Drop-free, Drug-free Therapies**

The use of heat and mechanical massage to clear obstructed meibomian glands has long been a cornerstone of MGD treatment. Currently, mechanical gland expression can be performed in the office using one of three techniques. Of note, none of these methods are covered by insurance in the US presently. The most sophisticated technology for meibomian gland expression is LipiFlow® (TearScience, Morrisville, NC; now Johnson and Johnson Vision), which uses computer-automated thermal pulsation and gentle pressure on both the inside and outside of the lid.6,7 LipiFlow requires single-use disposable cups and is the most expensive option.

MiBo ThermoFlo (MiBo Medical Group, Dallas, TX), which also uses thermoelectric heat and gentle pressure to receive blocked glands, works only the outside of the lid. It does not require a disposable interface and costs less to perform. My colleague Leslie O’Dell, OD, and I conducted a case series on MiBo ThermoFlo use among 11 subjects with bilateral MGD, treating one eye using the untreated eye as a control. Treated eyes showed significantly improved meibomian gland expression and secretion scores at one month following a single treatment; however, SPEED and OSDI scores were not significantly changed from baseline.8

A third technique is basic in-office manual expression by the eyecare provider, which, when properly performed, yields good results.9 Using a study design similar to the MiBo ThermoFlo study mentioned above, Dr. O’Dell and I investigated the efficacy of manual expression via a case series.10 We used an eyelid warming mask followed by manual expression using Maskin® Meibum Expressor (Rhein Medical, St. Petersburg, FL) on 24 individuals with chronic MGD. We observed significant improvement in SPEED and OSDI scores on treated eyes at 2 weeks and 1 month following a single treatment; objective measures of meibum secretions were not significantly improved, however.

Manual expression is the tool I use on MGD patients in my practice. A key to performing the procedure successfully is to warm the lid thoroughly to liquefy the meibum (heat masks can be used,) then immediately express the glands (on the pre-warmed side alone), observing closely for quality and expressibility. (A mnemonic device is LEO: liquefy, express, observe). Once upper and lower lids are completed on one side, the sequence can be repeated—starting with warming—on the other side. Attempting to express glands plugged with solid meibum can be painful for patients and is discouraged.11 Some of my colleagues

### Key Issues in Ocular Surface Disease

**STATEMENT OF NEED**

Although sometimes used as a synonym for dry eye disease, the term “ocular surface disease” refers to a cluster of anterior eye disorders that includes dry eye (evaporative or due to tear insufficiency), bacterial and viral infections, blepharitis, meibomian gland dysfunction, allergic conjunctivitis, corneal surface problems associated with glaucoma treatment, and the ocular manifestation of systemic inflammatory diseases and endocrine disorders (e.g., Sjögren’s syndrome, arthritis, and thyroid disease). While prevalence data vary considerably based on the population studied and disease definition, all of these conditions are common.1,2

In addition, they share pathogenic mechanisms, have overlapping clinical signs and symptoms, and are oftencomorbid.3 For example, allergic conjunctivitis, blepharitis and Sjögren’s syndrome—the dry eye disease—are inflammatory conditions that affect the ocular surface and share a number of symptoms, including discomfort, itching, dryness, and irritation.4,5

Diagnosis and treatment of ocular surface disease are clearly important, but they are rendered difficult by a number of factors: the frequency of comorbid conditions with similar signs and symptoms; incomplete understanding of the underlying pathogenesis; frequently poor correlation between signs and symptoms; occasional systemic disease as an underlying factor; and the absence of simple, clear diagnostic tests. Even after diagnosis, adherence to best practice in patient management is complicated by the number of agents available and competing claims for them in the marketplace.

Each installment of Key Issues in Ocular Surface Disease will look at two important topics in the management of ocular surface disease in order to support optometrists’ clinical reasoning and decision-making abilities and navigate the growing body of sometimes contradictory evidence on ocular surface disease. The benefits are substantial: accurate diagnosis and effective treatment of ocular surface disease will contribute greatly to patient comfort and satisfaction, help patients enjoy comfortable contact lens wear, and significantly enhance outcomes in cataract and corneal refractive surgery.

### References


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levels and following blood levels on the value of assessing baseline blood PUFA (Courtesy of Leslie O’Dell, OD, FAAO) is well accepted and generally well tolerated among DED experts and is a mainstay of treatment.14 Further, the knowledge around the most appropriate treatment to prescribe is complex, it is now accepted that inflammation plays a role; an elevated omega-6 to omega-3 fatty acid ratio may contribute to inflammation and meibum compositional imbalances. Supplementation with various combinations of oral omega-3 and omega-6 PUFAs has been shown to reduce signs and symptoms of DED.14

Although the pathophysiology of DED is complex, it is now accepted that inflammation plays a role; an elevated omega-6 to omega-3 fatty acid ratio may contribute to inflammation and meibum compositional imbalances. Supplementation with various combinations of oral omega-3 and omega-6 PUFAs has been shown to reduce signs and symptoms of DED.14 Despite growing interest and research on PUFA supplementation as DED treatment, there are holes in our knowledge around the most appropriate form, dose, composition, and length of treatment to prescribe.14 Further, the value of assessing baseline blood PUFA levels and following blood levels on treatment have not been investigated. This points to a significant flaw in how we currently prescribe nutritional supplements for our DED patients—we assume they each have PUFA ratios characteristic of the standard westerner; but surely some with better dietary habits or perhaps a different genetic makeup have more balanced blood levels and are not great candidates for PUFA supplementation. Luckily, a soon-to-be-completed NIH-funded study—the DREAM study [https://clinicaltrials.gov/show/NCT02128763]—may provide some answers and improve the precision of nutritional supplement prescribing. The DREAM study is a phase 3, multi-center, placebo-controlled trial of patients with DED undergoing treatment with dietary omega-3 fatty acid supplementation; it is notable for its size and for following PUFA blood levels, among other standard DED metrics.15

**Therapies in Development**

**Intranasal Tear Neurostimulation**

Neurostimulation is an FDA-sanctioned medical strategy for a range of neurologic and nonneurologic disorders, including headache, pain, stroke, spinal cord injury, incontinence and rheumatoid arthritis.16 Intranasal tear neurostimulation (ITN) is a novel mechanism for DED treatment that takes advantage of peripheral neural pathways between the nasal mucosa and tear film-supporting glands and cells. Nasolacrimal activation, in theory, should increase the volume of aqueous, proteins, and electrolytes in tears (from lacrimal glands); tear lipids (from meibomian glands); and mucins (from conjunctival epithelial goblet cells).

Thus far, some research is bearing this out. Animal studies have associated ITN with increased aqueous volume, decreased tear osmolarity, and increased tear protein and lipid production.17,18 Small-scale studies of TrueTear™ (Allergen, Parsippany, NJ)—a handheld ITN prototype currently in limited rollout in the US—have shown increased aqueous production (assessed by Schirmer scores and tear meniscus height) as well as reduced symptoms and conjunctival and corneal staining associated with DED.16,19 Separate studies of TrueTear in DED patients have demonstrated meibomian gland morphologic change (consistent with the release of meibum), augmented lipid secretion and lipid layer thickness, and goblet cell degranulation and increased mucin production.20,24 Neurostimulation is not effective in all patients. Assuming the product becomes more widely distributed, a simple in-office test can identify patients with a strong nasolacrimal reflex who are more likely to respond to ITN. Instruct the patient to place a cotton bud into his or her nose and push gently into the middle turbinate. If tears well up (typically at the lower lid) after a few seconds, then neurostimulation is more likely to work.

**IPL**

The delivery of high intensity, polychromatic light—intense pulsed light (IPL)—has long been used in dermatology as a “photofacial” for cosmetic lightening of sun spots, telangiectasia, and other forms of skin hyperpigmentation. An observation that rosacea patients treated with IPL (on the skin below the lower lids and across the bridge of the nose) saw improvements in their DED
symptoms has prompted interest in the therapeutic potential of IPL in MGD across patient types. A 2015 study by Craig and coworkers showed that IPL on inferior periorcular skin in mild to moderate MGD patients (N = 28) demonstrated improved lipid quality and tear breakup time (TBUT) in treated eyes compared with baseline and untreated eyes. In a separate study of patients with moderate to severe MGD with or without comorbid rosacea, IPL used in conjunction with meibomian gland expression resulted in significantly improved symptoms (assessed by SPEED) and signs of MGD (meibomian gland score and TBUT) and DED (tear osmolarity and corneal staining); in this study, lipid layer thickness was unchanged. How IPL works against DED is not clear. Proposed theories include thrombosis of abnormal blood vessels, liquefying meibum, and/or reducing epithelial turnover. Some contend that IPL’s mechanism involves the eradication of the mite Demodex, a mediator of blepharitis and MGD that commonly colonizes periorbital skin in patients with rosacea. Drawbacks of IPL include that it can only be performed in fair-skinned patients, and treatment must be confined to the lower lid. Also, IPL carries risk to the iris if the eye is not properly protected during treatment.

Radio Frequency

Radio frequency (RF) for the treatment of DED also stemmed initially from an observation that patients who underwent RF for cosmetic purposes reported an observation that patients who underwent RF for cosmetic purposes reported significantly greater improvement in symptoms compared with sham treatments. Although the mechanism is not fully understood, RF energy applied to skin has been shown to warm tissues, induce collagen remodeling and improve skin elasticity. An RF thermistor in development, ThermiEyes™ (Thermi LLC, Irving, TX) has been associated with improved symptoms and some improved signs in early studies of patients with DED and periorbital wrinkling.

Botulinum Toxin

Botulinum toxin A (BTA) injection (Botox; Allergan, Parsippany, NJ) into periorcular muscle has been shown to temporarily decrease lacrimal drainage comparable to punctal plugs. In a nonrandomized study among patients with severe DED (N = 60), those treated with BTA had fewer and milder side effects (shampoo in their eyes while showering in 33%, unimproved foreign body sensations and increased tearing in 17%) compared with those receiving punctal plugs (plug extrusion in 33%, continuous irritation and conjunctival erosion in 17%). Patients in the BTA group had higher rates of patient satisfaction. In a separate study, healthy patients undergoing LASIK reported greater overall satisfaction when BTA injection was used postoperatively compared with punctal plug. More research is needed in this area before the practice is embraced by practitioners in the US.

Conclusion

Current nonpharmacologic modalities—including nutritional supplementation and meibum expression—are integral to the management of DED. New methods with novel mechanisms of action are being investigated.

Milton M. Hom, OD, FAAO, is in private practice in California. He has received research support from Allergan and Kala Pharmaceuticals and is a consultant for Bausch + Lomb and Shire. Medical writer Noelle Lake, MD, assisted in the preparation of this manuscript.

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Systemic Autoimmunity and Dry Eye Disease

Jillian Ziemanski, OD, MS, FAAO

Systemic autoimmune diseases are becoming more common in industrialized nations. Dry eye may be the first sign of a more widespread inflammatory condition.

Dry eye (DED) stems from imbalances within the lacrimal functional unit affecting the tear film, ocular surface, and periocular tissue. In a minority of patients, however, DED may be related to an underlying systemic inflammatory or autoimmune (AI) condition, such as Sjögren’s disease, rheumatoid arthritis (RA), or systemic lupus erythematosus (SLE). Dry eye may be the presenting symptom in any of these inflammatory or AI conditions. Thus, eye care providers do well to have a working knowledge of the ocular signs and symptoms of systemic diseases; have a means for routine systemic disease screening and initial evaluation; and feel confident managing AI-related ocular surface conditions.

Etiopathogenesis

Autoimmune etiopathogenesis is not fully understood but may involve a combination of genetic, hormonal, environmental, and even dietary factors. A widely cited theory suggests that the stage is set for autoimmunity when a genetically susceptible individual encounters some form of environmental exposure, possibly a virus, bacterium or toxic pollutant; then, the body mounts an immune defense that “erroneously” targets human tissue bearing similarly structured proteins or nucleic acids, a process called “molecular mimicry.” Although definitive proof is lacking, Epstein-Barr virus (EBV), hepatitis C virus, human T-cell leukemia virus type 1 (HTLV-1), and Helicobacter pylori have been proposed as pathogens responsible for the underlying immune misdirection in some instances of AI disease.

Gut microbiota imbalances (or dysbiosis) have also been implicated in the pathogenesis of inflammatory and AI diseases. The gut microbiota is the vast, dynamic collection of commensal organisms that reside in the human gut and that have far-reaching influence on immune, neurologic, and endocrine systems. Dysbiosis may occur in the setting of a fiber-deficient diet, psychological stress, antibiotic and xenobiotic (synthetic chemical) exposures, and other factors, any of which may contribute AI pathogenesis and may at least partially explain a general trend in rising AI disease incidence in recent decades.

Systemic Diseases and DED

Sjögren’s syndrome affects an estimated 2 to 4 million individuals in the US, and the ratio of women to men affected is 9 to 1. Primary Sjögren’s is thought to result from lymphocytic infiltration into the salivary and lacrimal glands. Patients may experience progressively worsening dry eye symptoms for months to years at presentation; many also have xerostomia (dry mouth), other xerotic symptoms such as dry skin, and constitutional symptoms such as fatigue and malaise. Sjögren’s syndrome may also affect the lungs, kidneys, gastrointestinal tract, and nearly any extra glandular site.

About 60% of patients with AI-mediated DED due to a disease other than Sjögren’s—such as RA, SLE, mixed connective tissue disease, or systemic sclerosis—carry a somewhat confusing designation of “secondary” Sjögren’s syndrome. The extent of pathogenic similarity between primary and secondary Sjögren’s cases is not clear.

Among patients with RA, DED is prevalent and likely significantly underdiagnosed. A single-center prospective study of adult RA patients presenting to a non-eye care clinic (n=286) by Yumori and coworkers showed that DED of at least level 1 severity (DEWS modified severity scale), as assessed by Ocular Surface Disease Index (OSDI), tear osmolarity (TO), tear break-up time (TBUT), corneal/conjunctival staining, and Schirmer testing (ST), was 96%; and 34% of RA patients had DED of at least level 3 severity. Among patients with at least level 1 severity DED, only 44% reported having been diagnosed with DED.

Autoimmune disease may affect ocular surface via inflammatory, infiltrative, or lid-based pathology.

Work up DED that is moderate-to-severe, poorly responsive to treatment, or associated with extraocular signs (ie, mouth dryness, fatigue, arthritis).

Familiarize yourself with the ocular staining score used for diagnosis of Sjögren’s syndrome.

All eye care patients should have ROS; include specific questions about mouth dryness, constitutional symptoms, and arthritis.

ODs are well positioned to detect and diagnose autoimmune DED.
glands producing aqueous-deficiency DED. However, in addition, meibomian gland disease (MGD) complicates a substantial proportion of cases, resulting in a “mixed” (aqueous deficiency plus evaporative) pattern of DED. In my experience, evaporative DED (with or without concomitant aqueous deficiency) is a very common pattern among patients with systemic AI diseases. It is hypothesized that aqueous-deficiency DED produces downstream effects that negatively affect the meibomian glands, triggering a self-perpetuating cycle of inflammation, epithelial cell turnover, gland dysfunction, and gland obstruction. Also, patients with AI are subject to the same established ocular surface stressors (e.g., computer use, low humidity, air conditioning, cigarette smoke, certain drugs such as anticholinergics) as the general population, but having an underlying AI disease may limit their ability to restore the integrity of the ocular surface. It is also possible that an evaporative component may relate to risk factors that are completely unrelated to their AI disease. Probably, both of these mechanisms contribute to MGD in patients with autoimmunity, especially since extensive digital device use—and its effects on meibomian glands and the tear film—is now our cultural norm (Figure 1).

The bottom line here is that patients with an underlying systemic illness may present with any DED type—aqueous deficiency, evaporative, or mixed. And considering the imprecision of Schirmer testing for detecting aqueous deficiency, providers should not dismiss the possibility of an underlying AI disease based on an absent or undetectable aqueous deficiency.

The typical presentation of AI or Sjögren’s-related DED is pretty much identical to non-Sjögren’s DED. Patients may complain of ocular symptoms that get worse over the course of a day, for example, irritation, burning, stinging, grittiness, foreign body sensation, itching, ocular fatigue, or visual disturbance. The dilemma faced by eye care providers is when to suspect and evaluate for a systemic disease. An important clue is disease severity and longevity.

**Review of Systems**

A review of systems (ROS) is an efficient screen for symptoms patients might not otherwise volunteer; a “positive” ROS may indicate a comorbidity or underlying illness. For patients with DED, it is worthwhile to include questions in the ROS related to Sjögren’s and other connective tissue diseases. In my practice, I typically will ask patients the questions in Table I, although it is by no means an exhaustive list.

**Diagnosis**

According to the American College of Rheumatology, a diagnosis of Sjögren’s syndrome can be made when at least 2 of the following 3 tests are positive:

- Serum autoantibodies: anti-SSA (Ro) OR anti-SSB (La) OR both ANA and RF
- Lip biopsy showing focal lymphocytic sialoadenitis
- Ocular Staining Score \( \geq 3 \)

The ocular staining score ranges from 0 to 12 and is a specific grading system applicable to the diagnosis of Sjögren’s syndrome. It requires evaluation of lissamine green staining of the nasal and temporal bulbar conjunctiva, as well as fluorescein staining of the cornea. Each of the three regions is graded on a scale of zero to three (based on the number of dots) and then summed per eye. Extra points are given if there are

### TABLE I Sample ROS for Patients with DED

<table>
<thead>
<tr>
<th>Question</th>
<th>Disease Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you had recurrently or persistently swollen salivary glands as an adult?†</td>
<td>Sjögren’s primarily, but also sarcoidosis</td>
</tr>
<tr>
<td>Do you frequently drink liquid to aid in swallowing dry food?*†</td>
<td>Sjögren’s primarily, but also sarcoidosis</td>
</tr>
<tr>
<td>Do you have joint or muscle pain?</td>
<td>autoimmune in general</td>
</tr>
<tr>
<td>Do you have generalized fatigue?</td>
<td>autoimmune in general</td>
</tr>
<tr>
<td>Have you had intermittent redness or burning of the face?</td>
<td>rosacea</td>
</tr>
<tr>
<td>Have you had recent weight loss, anxiety, hand tremor, sensitivity to heat?</td>
<td>Graves’ disease</td>
</tr>
<tr>
<td>Do you have a chronic, dry cough or shortness of breath?</td>
<td>sarcoidosis</td>
</tr>
</tbody>
</table>

*Recommend using this question judiciously, as frequently elicits “false positive” response

any patches of confluent corneal staining (+1), central corneal staining within the pupillary area (+1), or the presence of filaments (+1). It is important to note that meeting this criterion for ocular staining is not done with the traditional corneal staining grades that most eye care providers are familiar with.

Patients suspected of having Sjögren’s or other AI disease should undergo a full DED workup, including standard tests and quantification of ocular surface staining. Ocular surface inflammation may be assessed via InflammaDry® (RPS Diagnostics, Sarasota FL); but a negative test does not rule out an inflammatory condition. Meibography imaging is valuable in patients suspected of having MGD (Figure 2). Depending on state laws on scope of practice, eye care providers may order the appropriate bloodwork and may therefore be fully empowered to independently diagnose Sjögren’s syndrome. If staining and antibodies are affirmative, a diagnosis of Sjögren’s syndrome can be made prior to referral. Alternatively, providers may choose to refer patients with suspected Sjögren’s or AI disease to a rheumatologist for diagnosis.

**Treatment**

It is important to set expectations from the outset that effective DED treatment requires daily effort on the part of the patient. In particular, moderate to severe DED—whether related to an underlying AI disease or not—requires an aggressive treatment strategy comprised of multiple therapies. In addition to standard DED therapies (eg, warm compresses, lid hygiene, and ocular surface lubricants), topical ocular anti-inflammatory and/or immunomodulatory agents, punctal plugs, and other therapies are often needed to control moderate to advanced Sjögren’s or non-Sjögren’s DED.

Poor response to optimized ocular treatment may indicate a lack of control of the underlying systemic disease; re-evaluation by rheumatology and adjustment of systemic medications may be helpful. That said, research has shown that, while generally effective in the treatment of arthritis and other systemic manifestations of Sjögren’s, to date, systemic immunomodulatory therapy has not been shown to be effective for treatment of Sjögren’s-related DED.

**Conclusion**

Eye care providers should stay alert for signs and symptoms of an underlying systemic autoimmune or connective tissue disease in their patients with DED. These patients will likely require more intensive and aggressive DED treatment and a team approach to their care.

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1. Which of the following systemic diseases is NOT associated with DED?
   A. Lupus
   B. Sjögren’s syndrome
   C. Autoimmune thyroiditis, such as Graves’ disease
   D. All are associated with DED

2. Your workup of a patient with severe DED, difficulty swallowing, and intermittent generalized joint pain reveals the following bloodwork and ocular staining results. Which patient’s diagnosis is in question and should be referred for lip biopsy?
   A. Anti-Ro and Anti-La negative; ANA and RF positive; Ocular Staining Score = 3
   B. ANA positive; Anti-Ro, Anti-La, and RF negative; Ocular Staining Score = 4
   C. Anti-Ro, Anti-La, ANA and RF negative; Ocular Staining Score = 2
   D. Anti-Ro positive; Anti-La, ANA and RF negative; Ocular Staining Score = 4

3. Which of the following DED therapies in development were NOT first used in dermatology?
   A. Intranasal tear neurostimulation
   B. Radiofrequency
   C. Intense pulsed light
   D. None of the above are used in dermatology

4. According to research cited in this article, compared to older individuals, individuals younger than 40 to 45 years of age:
   A. Check their cell phones more frequently
   B. Spend more total daily time on phones and computers
   C. Are better at multitasking
   D. A and B

5. Which of the following is NOT affected by staring at a computer?
   A. Interblink interval
   B. Lacrimal drainage
   C. Blink frequency
   D. Blink completeness

6. Which of the following is NOT an appropriate approach to meibum expression?
   A. Thermoelectric heat/mechanical expression instrument followed by manual expression at subsequent visits
   B. Lid warming followed by manual expression
   C. Manual expression alone
   D. All of the above are appropriate approaches

7. How are meibomian glands NOT hypothesized to be affected by aqueous-deficiency DED?
   A. Epithelial cell turnover
   B. Keratoconus
   C. Inflammation
   D. Gland dysfunction

8. Which of the following statements is true according to the study of DED prevalence in patients with RA (Yumori et al) cited in this article?
   A. About half of RA patients had at least level 1 severity DED
   B. About half of RA patients with at least level 1 severity DED were undiagnosed
   C. About a quarter of RA patients had level 2 severity DED
   D. A and B

9. ITN, a technology in development, has been associated with which of the following outcomes in patients with DED?
   A. Mucin production
   B. Aqueous production
   C. Lipid production
   D. All of the above

10. Which of the following terms describes a theory regarding autoimmune pathogenesis?
    A. Molecular mimicry
    B. Xenobiotic deficiency
    C. Mirror neuron effect
    D. Rheumatic antipathy

HOM REFERENCES continued from page 4