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ORIGINAL RESEARCH

Presence or absence of ocular surface inflammation directs clinical and therapeutic management of dry eye

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Background: The presence of clinically significant inflammation has been confirmed in the tears of 40%–65% of patients with symptoms of dry eye. Ocular surface inflammation may lead to tear film instability, epithelial cell irregularities, and permeability, resulting in chronic symptomatic pain and fluctuating vision as well as negative surgical outcomes.

Patients and methods: A retrospective single center medical chart review of 100 patients was conducted. All patients were tested with the InflammaDry test to determine if patients exhibited elevated levels of matrix metalloproteinase 9 (MMP-9). InflammaDry-positive patients were started on a combination of cyclosporine 0.05% twice daily, 2,000–4,000 mg oral omega-3 fatty acids, and frequent artificial tear replacement. InflammaDry-negative patients were started on 2,000–4,000 mg of oral omega-3 fatty acids and frequent artificial tear replacement. Each patient was retested at ~90 days. A symptom questionnaire was performed at the initial visit and at 90 days.

Results: 60% of the patients with dry eye symptoms tested positive for elevated MMP-9 at the initial visit. 78% of all patients returned for follow-up at ~90 days including 80% (48/60) of the previously InflammaDry-positive patients and 75% (30/40) of the previously InflammaDry-negative patients. A follow-up symptom questionnaire reported at least 75% symptomatic improvement in 65% (31/48) of the originally InflammaDry-positive patients and in 70% (21/30) of the initially InflammaDry-negative patients. Symptomatic improvement of at least 50% was reported in 85% (41/48) of previously InflammaDry-positive patients and 86% (26/30) of previously InflammaDry-negative patients. Following treatment, 54% (26/48) of previously InflammaDry-positive patients converted to a negative InflammaDry result.

Conclusion: Identifying which symptomatic dry eye patients have underlying inflammation may predict patient responses to treatment and influence clinical management strategies.

Keywords: dry eye, inflammation, MMP-9, cyclosporine, diagnosis, treatment

Introduction

Dry eye is a multifactorial disease that is related to the relationship between the amount of tears produced, rate of tear evaporation, goblet cell density, and the presence or absence of inflammation. The discordance between symptoms, clinical signs, and diagnostic test results makes the clinical management and treatment of this condition challenging.[1] Only 40%–65%, or approximately half of patients with symptoms of dry eye have clinically significant inflammation, with or without the presence of meibomian gland dysfunction (MGD).[2–6] The presence of inflammation may lead to chronic symptomatic pain and fluctuating vision as well as negative surgical outcomes. Identifying the presence or absence of ocular surface inflammation helps guide therapeutic decision making.[7]

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Desiccating stress to the ocular surface epithelium activates the mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB pathways, which stimulate production of epithelial-derived inflammatory mediators such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, IL-8, and matrix metalloproteinase (MMP)-9.[8–16] MMP-9 is an ideal biomarker for inflammation since it elevates early, is stimulated by IL-1, TNF-α, IL-6, IL-8, IL-17,[8–11,13–17] catalyzes further development of IL-1 and TNF-α,[13] and accumulates as part of a persistent cycle of inflammation. Moreover, MMP-9 destabilizes the tear film and directly contributes to corneal barrier dysfunction by breaking down tight junctions, causing epithelial cell desquamation, and facilitating inflammatory cell migration, which ultimately leads to corneal staining and rapid tear break up times.[8,13,15,16] Elevation in MMP-9 was shown to precede the development of corneal staining and contribute to the instability of the tear film in 30% of patients, resulting in pain and fluctuating vision.[6]

Downregulation of MMP-9 expression is associated with improvement in ocular surface epithelia.[18] Further, MMP-9 knockout mice are resistant to developing dry eye.[19] Normal MMP-9 levels range from 3 to 41 ng/mL.[20,21] 53% of symptomatic dry eye patients have MMP-9 levels elevated to ≥40 ng/mL.[6] InflammaDry (RPS Diagnostics; Sarasota, FL, USA) is a rapid in-office test that detects elevated MMP-9 in tears.

Most dry eye testing methods such as tear breakup time (TBUT), Schirmer tear testing, tear osmolarity, and diagnostic imaging methods such as inferometry, meibomography, corneal topography, and ocular coherence tomography provide valuable information to help characterize patients as evaporative or aqueous deficient but cannot predict which patients have clinically significant ocular surface inflammation.[22] However, the presence of corneal and/or conjunctival staining with a vital dye is a clinical indicator of inflammation and directly correlates to the levels of inflammatory mediators and MMP-9. Clinical studies based on a positive ocular surface disease index (OSDI) reveal that 8%–57% of symptomatic dry eye is associated with fluorescein or lissamine green conjunctival or corneal staining.[23–25] Staining has been shown to occur in only 65% of patients with moderate-to-severe dry eye.[26] Moreover, outside the clinical trial setting, staining and TBUT are not typically performed accurately in busy clinical practices. Staining and TBUT must be measured prior to the use of topical anesthetics, which induce a rapid TBUT and epithelial staining.[27,28]

Lanza et al enrolled 110 patients with dry eye symptoms and measured Schirmer levels, TBUT, osmolarity, and MMP-9.[22] Thirty-nine percent were positive for elevated levels of MMP-9. No statistical difference was found in the symptoms or signs of dry eye patients that tested positive or negative for elevated MMP-9.[22] Thus, it is not possible to identify patients who have ocular inflammation based on a profile of their symptoms or signs.

To further investigate the dry eye population, a clinical diagnostic and treatment protocol was implemented within a large multicenter group practice in 2015. The research hypothesis was that targeting anti-inflammatory therapy for patients with confirmed underlying ocular surface inflammation might lead to improved patient symptoms and signs while limiting unnecessary therapy.

Methods

A retrospective single center medical chart review of 100 patients seen over the preceding 180 days was conducted in a large multispecialty private ophthalmology practice in Southwest Florida. A chart review was performed to identify the most recent 100 patients who presented with symptoms of dry eye, were tested with InflammaDry, were started on therapy, and were seen in follow-up ~90 days later. According to the Shulman Institutional Review Board (Cincinnati, OH, USA) exemption classifications, this retrospective study was deemed exempt from institutional review board approval and patient consent.

Data collected included age, gender, InflammaDry test results before and after treatment, and a dry eye symptom questionnaire results before and after treatment.

The InflammaDry test was performed as per the manufacturer's instructions to determine if patients exhibited elevated levels of MMP-9, which represented clinically significant ocular surface inflammation. The InflammaDry test required an ophthalmic technician to collect a tear sample from the patient's palpebral conjunctiva. The palpebral conjunctiva was gently dabbed 6–8 times in multiple locations, releasing the lid after every 2–3 dabs to allow the patient to blink. Then, the sampling fleece was allowed to rest against the conjunctiva for an additional 5 seconds until the sampling fleece was saturated with tears (10 μL) and either demonstrated a pink color or appeared glistening. After obtaining the sample, the sample collector was assembled onto the test cassette. The assembled test was activated by dipping the absorbent pad into a buffer solution for ~20 seconds. After 10 minutes had elapsed, the test was interpreted. The presence of 1 blue line and 1 red line in the test's result window was indicative of a positive test result (MMP-9 ≥40 ng/mL). The intensity of the red line is directly related to the amount of MMP-9 present; thus, mild dry eye is associated with fainter result lines than more severe dry eye. The presence of a red line of any intensity confirmed the presence of elevated

MMP-9. One blue control line indicates a negative test result (MMP-9 <40 ng/mL).[21]

Each patient who tested InflammaDry-positive was started on topical cyclosporine 0.05% (Restasis; Allergan, Irvine, CA, USA), oral omega-3 fatty acids twice daily for a total of 2,000–4,000 mg, and frequent artificial tears. All patients who tested negative were recommended to use oral omega-3 fatty acids at a dose of 2,000–4,000 mg twice daily and frequent artificial tears.

All patients completed a symptom questionnaire derived from the OSDI at the initial visit and at the follow-up visit ~90 days later. All symptomatic patients identified with dry eye symptoms were included so that a wide range of severity was included in the treatment analysis. Each patient was tested with the InflammaDry test at the initial visit and follow-up visit. The patients were asked to provide an overall grade to their clinical symptomatic improvement since starting therapy compared to their initial visit from no improvement to complete resolution of symptoms based on 25% improvement increments (eg, none or minimal symptomatic improvement of ≤5%, modest symptomatic improvement of 6%–24%, moderate symptomatic improvement of 25%–49%, significant improvement of 50%–74%, and dramatic symptomatic improvement of 75%–100%). Patients treated with topical cyclosporine for conditions other than dry eye were excluded. Patients using artificial tears more than twice daily prior to the initial visit were excluded from the review.

Results

A total of 100 charts were examined. Seventy-two percent (72/100) of patients were females with a mean age of 64 years and age range was from 17 to 89 years. Sixty percent of the patients with dry eye symptoms tested positive with the InflammaDry test for elevated MMP-9 at the initial visit.

Only 78% (78/100) of the patients returned for follow-up at ~90 days including 80% (48/60) of the previously InflammaDry-positive patients and 75% (30/40) of the previously InflammaDry-negative patients. Repeat InflammaDry testing and symptom questionnaires were performed at the follow-up visit. Eight percent (5/60) of patients started on cyclosporine could not tolerate it because of stinging and were excluded from calculations.

Sixty percent (29/48) of the initially InflammaDry-positive patients and 63% (19/30) of the initially InflammaDry-negative patients reported at least 75% improvement in symptoms. Eighty-five percent (41/48) of the initially InflammaDry-positive patients reported at least 50% improvement, while 86% (26/30) of the initially InflammaDry-negative patients reported at least 50% improvement. The remainder of the patients reported between 6% and 49% improvement in symptoms (Table 1). The follow-up symptom questionnaire reported that at least modest symptomatic improvement was achieved in 100% (78/78) of follow-up patients.

Following treatment, 54% (26/48) of previously InflammaDry-positive patients converted from a positive to a negative InflammaDry result. Of the patients who converted to negative, 88% (23/26) reported at least 75% improvement in symptoms, while the remaining 12% (3/26) reported at least 50% improvement in symptoms. Of the 46% (22/48) of initially InflammaDry-positive patients who remained positive at the 90-day follow-up visit, 36% (8/22) reported 6%–49% symptomatic improvement. In symptomatically improved patients who remained InflammaDry-positive at 90 days, most demonstrated a less intense result line on the InflammaDry test, suggesting that the treatment was helpful but not adequate to lower the level of MMP-9 antigen below the cutoff threshold.[29] Six percent (2/30) of the previously negative patients became InflammaDry-positive at 90 days.

Discussion

Identifying symptomatic dry eye patients with underlying inflammation may predict patient response to treatment and influence patient management strategy recommendations including artificial tear replacement, punctal occlusion, or anti-inflammatory therapeutics such as a short course of corticosteroids, oral doxycycline, or long-term maintenance treatment with cyclosporine and/or lifitegrast (Xiidra; Shire,

Table 1 90-day follow-up symptom analysis

Metrics	90-day follow-up visit (N=78)	
	InflammaDry-positive at initial visit, %	InflammaDry-negative at initial visit, %
≥75% symptom improvement	60 (29/48)	63 (19/30)
≥50%–74% symptom improvement	25 (12/48)	23 (7/30)
≥25%–49% symptom improvement	10 (5/48)	7 (2/30)
≥6%–24% symptom improvement	6 (3/48)	3 (1/30)
≤5% symptom improvement	0 (0/48)	0 (0/30)

Lexington, MA, USA). As evidenced by prevalence studies using staining or point-of-care testing for MMP-9, clinically significant inflammation occurs in ~50% of symptomatic dry eye patients with or without the presence of meibomian gland dysfunction.[2–6] Because staining is often performed incorrectly and MMP-9 is induced by all of the primary mediators including IL-1β, TNF-α, IL-6, IL-8, IL-17, and tumor growth factor, early and throughout the inflammatory cascade, MMP-9 represents an ideal marker for ocular surface inflammation.[8–14,17,30]

The presence of ocular surface inflammation allows for a more targeted clinical management and therapeutic approach. Artificial tears provide palliative relief of eye irritation in patients with aqueous tear deficiency.[31] However, artificial tears do not significantly reduce MMP-9 levels,[31,32] prevent underlying inflammation, or reverse conjunctival squamous metaplasia in chronic dry eye.[31] Tong et al showed that MMP-9 levels are unchanged 3 weeks after punctal occlusion.[33] Punctal occlusion should be reserved for patients without ocular surface inflammation or performed after the inflammation is under control.[34,35]

Patients with confirmed inflammation benefit from chronic anti-inflammatory therapy.[36,37] Treatment with anti-inflammatory medications such as topical corticosteroids and cyclosporine decreases the production of inflammatory cytokines.[30,32,38–41] Moreover, both corticosteroids[42] and topical cyclosporine[43] lead to increased goblet cell density in tear dysfunction associated with non-Sjögren's and Sjögren's diseases. Treatment of dry eye with methylprednisolone and doxycycline was shown to preserve the tight junction network, increase corneal smoothness, preserve corneal barrier function, and lead to a reduction in the production and activity of MMP-9.[44] Doxycycline has been found to inhibit MMP-9 activity in human corneal epithelial cells[9] and may be used to treat MMP-mediated ocular surface diseases, such as rosacea, recurrent epithelial erosion, and sterile corneal ulceration.[45,46] Lifitegrast reduces the overall inflammatory response resulting from T-cell adhesion to endothelial cells before trans-endothelial migration to inflamed tissues as well as at the point of T-cell interaction with antigen-presenting cells.[47] These processes should result in decreased levels of pathogenic mediators and less inflammation on the ocular surface.[47] Similarly, elevated MMP-9 should identify populations that enhance liftegrast's therapeutic efficacy.

Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha linolenic acid (ALA) are the three omega-3 fatty acids that cannot be synthesized in the body and have to be supplemented in diet. EPA and DHA modulate prostaglandin metabolism toward anti-inflammatory prostaglandin synthesis due to competitive inhibition of the arachidonic acid pathway.[48] Omega-3 supplementation demonstrates an anti-inflammatory effect, inhibiting creation of omega-6 prostaglandin precursors, preventing apoptosis of the secretory epithelial cells in the lacrimal gland, and clearing meibomitis, which allows for a healthier lipid layer to protect the tear film and cornea.[49]

Therapeutic responses from topical anti-inflammatory agents do not result in significant clinical improvement in more than half the patients treated.[35,50] This is evidenced by moderate, or complete, regression of symptoms in only 43%, or 57%, respectively, of dry eye patients with delayed clearance following treatment with loteprednol.[51] Similarly, treatment with topical cyclosporine 0.1% for 6 months showed only moderate response to treatment in 39% of symptomatic dry eye patients.[50]

In contrast, in this retrospective study, significant clinical responses approached 85%–87% for >50% clinical improvement, which is significantly higher than previous studies. Enriching the treatment population by targeting only those patients with confirmed ocular surface inflammation may have led to improved outcomes. It is likely that symptomatic dry eye patients who do not respond to anti-inflammatory agents are the same populations that do not have ocular surface inflammation present.

However, 46% of patients demonstrated elevated levels of MMP-9 despite targeted therapies. Patients with chronically elevated MMP-9 were associated with patients reporting less clinical benefit. Similar to managing systemic diseases such as hypertension, diabetes mellitus, and hypertriglyceridemia, it is likely that these patients require an additional anti-inflammatory therapy and not substitution with a different anti-inflammatory treatment. Additional treatments may also include targeting any meibomian gland dysfunction or blepharitis. One option is to increase the frequency of cyclosporine 0.05% to 3–4 times daily.[52] Alternatively, a low potency steroid such as fluorometholone or loteprednol may be added to the cyclosporine regimen to achieve adequate inflammatory control. The addition of the steroid to the cyclosporine, rather than the replacement of the cyclosporine therapy, allows for decreased daily steroid dosing, which may reduce the risk for steroid-induced side effects. In the future, it is possible that cyclosporine and lifitegrast may be combined in patients refractory to a single topical agent (Figure 1). It is unlikely that liftegrast will work on cyclosporine failures as both medications inhibit similar inflammatory mediators.

Topical steroids may have the most potent and rapid anti-inflammatory action, which may be ideal prior to initiating

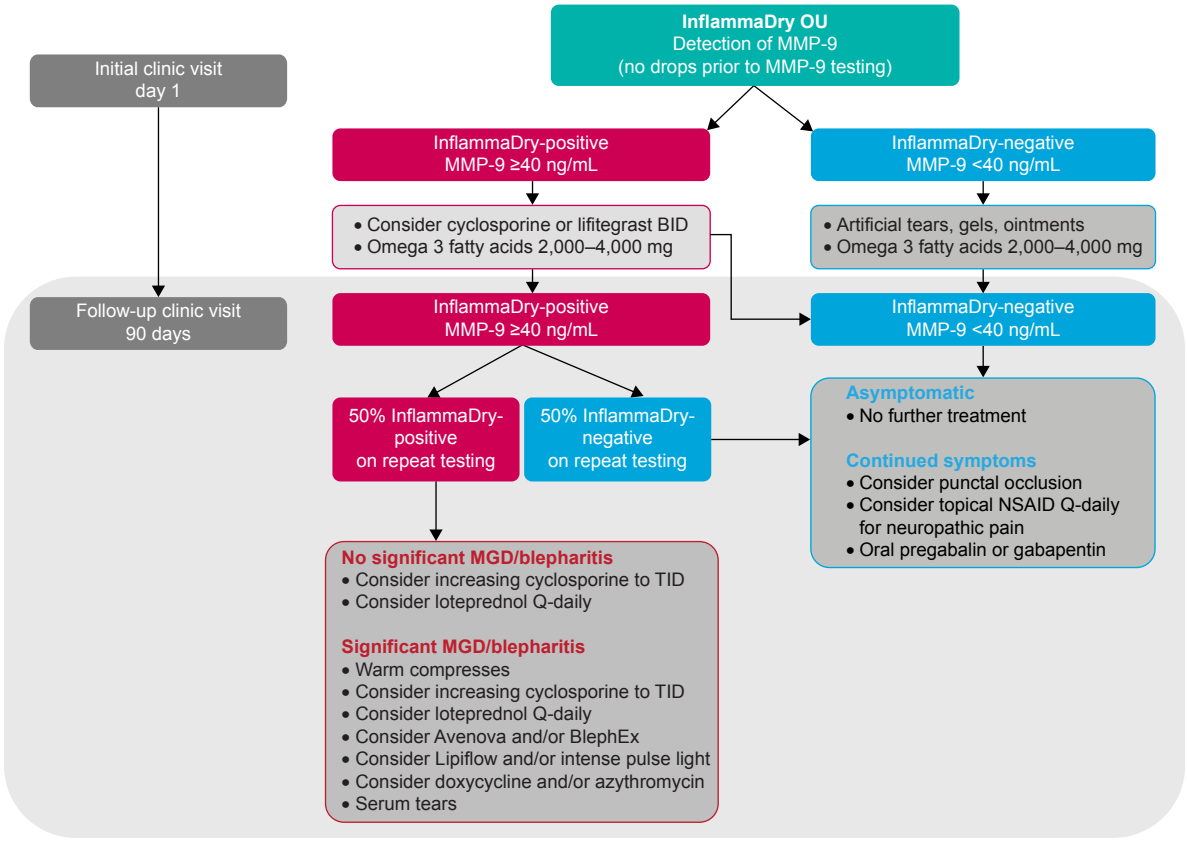


Figure 1 Dry eye clinical management and treatment protocol.
Abbreviations: BID, two times a day; MGD, meibomian gland dysfunction; MMP-9, matrix metalloproteinase 9; NSAID, nonsteroidal anti-inflammatory drug; TID, three times a day.

cyclosporine to reduce the sting[53] and for ocular surface optimization prior to obtaining kerotometry, aberrometry, and biometry. Long-term steroid treatment is not advisable because of the risk for cataract formation and increased intraocular pressure.[54] Cyclosporine has minimal side effects compared with steroids and may be used chronically without significant risk.[50,55,56] Coupled with oral omega-3 therapy, cyclosporine is effective and low risk as chronic anti-inflammatory therapy.

This study has several limitations. First, this was not a prospective randomized controlled therapeutic study and retrospective studies have inherent weakness. A future study should compare the efficacy of cyclosporine in both the InflammaDry-negative and -positive patients. Rigid periodic therapeutic monitoring throughout the study was not performed. In addition, 22% of patients did not return for the 90-day follow-up period, which could influence the reported clinical success rates. Finally, the omega-3 therapy was not standardized and its efficacy is influenced by bioavailability and absorption. Despite its limitations, this is the first study to demonstrate improved clinical outcomes based on treating a targeted symptomatic dry eye patient population with confirmed ocular surface inflammation.

Conclusion

MMP-9 is induced by key cytokines in the early stages of the inflammatory cascade and therefore is an ideal biomarker because its elevation confirms the presence of clinically significant ocular surface inflammation. Clinically significant inflammation is present only in approximately half of the patients with symptomatic dry eye. This is evidenced by <57% of all comer's studies revealing conjunctival or corneal staining[23–25] and the demonstration of only 39%–57%[50–51] symptomatic improvement found in clinical trials evaluating the efficacy of cyclosporine and loteprednol, respectively. Coupled with the results from this study, it suggests that identifying symptomatic dry eye patients with underlying inflammation may help predict patient responses to treatment and influence clinical patient management strategies.

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Disclosure

The author is an employee of RPS Diagnostics, the manufacturer of the InflammaDry test, and is a consultant to Allergan, the manufacturer of Restasis. The author reports no other conflicts of interest in this work.

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