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PRACTICAL MANAGEMENT OF INFLAMMATION IN DRY EYE

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List of Abbreviations

ADDE	Aqueous-deficient dry eye
APC	Antigen presenting cell
BAK	Benzalkonium chloride
CsA	Cyclosporine A
DED	Dry eye disease
DEWS	Dry Eye Workshop
EDE	Evaporative dry eye
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICAM	Intercellular adhesion molecule
IL	Interleukin
IL-1RA	IL-1 receptor antagonist
IFN-γ	Interferon-gamma
IOP	Intra-ocular pressure
IVCM	*in vivo* confocal microscopy
MGD	Meibomian gland disease
MMP	Metalloproteinase
OSDI	Ocular surface disease index
TBUT	Tear film break-up time
Th	T helper
TIMP	Tissue inhibitor of metalloproteinase
TFOS	Tear Film Ocular Surface
TGF-ß2	Transforming growth factor-beta 2

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DEFINITION OF DRY EYE DISEASE
ACCORDING TO THE TFOS-DEWS II

The definition of dry eye disease (DED) was recently updated by the TFOS-DEWS II as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface **inflammation** and damage, and neurosensory abnormalities play etiological roles" [1].

Two main forms of DED are considered: aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE). Generally, most patients with symptoms related to ocular surface disease suffer from variable combinations of both mechanisms. These mechanisms lead to hyperosmolar tissue damage that induces inflammation and causes a loss of both epithelial and goblet cells. Neurogenic inflammation is believed to play an important role in the onset and chronicity of ocular inflammation in DED [2,3]. These reactions at the ocular surface will manifest as decreased surface wettability, early tear film breakup and amplification of hyperosmolarity, all leading to a vicious perpetual cycle of DED [4, 5].

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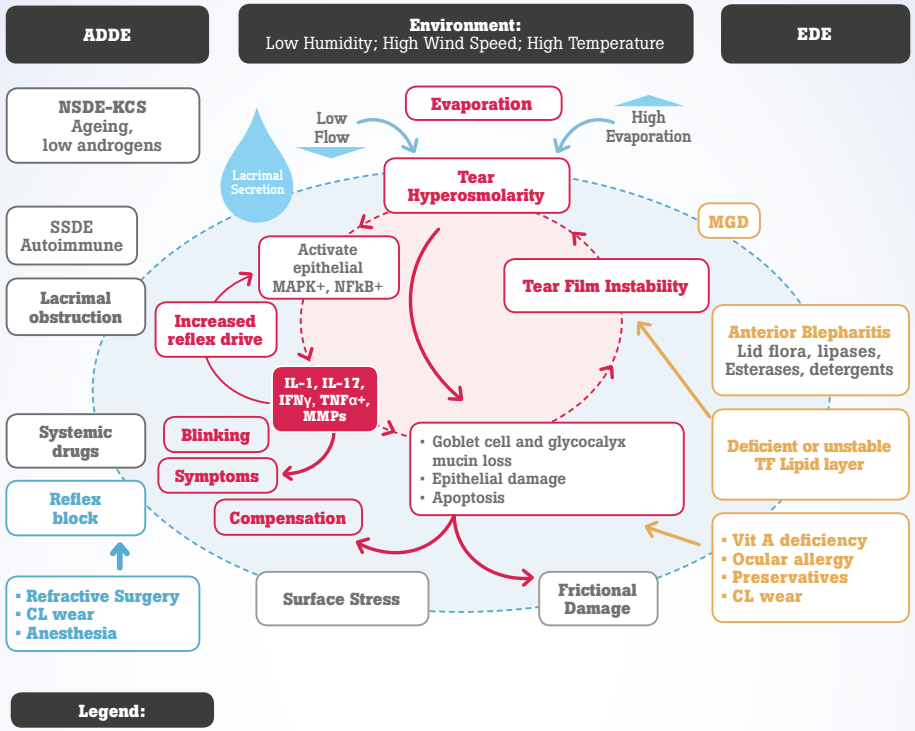
PATHOPHYSIOLOGY OF DRY EYE DISEASE

The pathogenesis of DED is not fully understood; however, inflammation is recognized as having a prominent role in the development and progression of this debilitating condition. Factors that adversely affect tear film stability and osmolarity can induce ocular surface damage and initiate an inflammatory cascade that generates innate and adaptive immune responses. In addition, the hyperosmolar-mediated epithelial damage causes exposure and chronic stimulation of corneal nerve endings which results in the release of neurotrophic factors affecting immune cell degranulation, blood flow and extravasation and to neurogenic inflammation on the ocular surface and within the lacrimal gland [2]. These immune-inflammatory responses lead to further ocular surface damage and the development of a self-perpetuating inflammatory cycle [2, 5, 6]. Inflammation is both a cause and effect of DED [7]. This vicious cycle reinforces itself with each repetition, leading to an increased severity in the clinical expression of the disease [8].

Role of Inflammation in Dry Eye Disease

In DED, the chronicity of the disease suggests a dysregulation of immune mechanisms leading to a circle of continuous inflammation, accompanied by alterations in both innate and adaptive immune responses [9]. Ocular surface immune homoeostasis is regulated by resident lymphocytes. Stress factors including environmental challenges, infections, endogenic stress, autoimmunity and genetic factors may disturb this finely-tuned homoeostatic balance and activate an acute inflammatory response [2].

Figure 1. The vicious dry eye cycle.



Legend:

IFNY: Interferon gamma
Il-1/-17: Interleukin -1/-17
KCS: keratoconjunctivitis sicca
MAPK: MAP kinase
MGD: Meibomian gland dysfunction
MMP: matrix metallopeptidase
NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells
NSDE: non-Sjögren dry eye
TFNα: tumour necrosis factor alpha

Ref: Adapted from TFOS DEWS II Pathophysiology report [4]

The innate immune response

Stress factors such as infections, environmental challenges or hyperosmotic stress may initiate innate inflammatory events. Corneal and conjunctival epithelia exposure induces the activation of signaling cascades which leads to the expression of pro-inflammatory cytokines and chemokines such as TNF-α, IL-1ß, IL-6 and IL-8, and matrix degrading proteases such as metalloproteinase (MMP)-9 and MMP-3 by corneal and conjunctival epithelial cells. This pro-inflammatory milieu upregulates the expression of inflammatory effectors such as HLA-DR and adhesion receptors facilitating the recruitment and migration of inflammatory mediators. These events contribute to amplifying and perpetuating the innate inflammatory responses resulting in cellular and tissue damage [2].

The adaptive immune response

Pro-inflammatory cytokines produced by epithelial cells activate immature resident antigen-presenting cells (APCs) (mainly dendritic cells) on the ocular surface. Mature APCs migrate to the regional lymph nodes and initiate an adaptive immune response by priming naive CD4+ T-cells including T helper (Th)1 and Th17 cells.

Through activated angiogenesis and lymphangiogenesis, these inflammatory cells traffic back to the ocular surface where Th1-secreted interferon-gamma (IFN-Y) and Th17-secreted IL-17 increase cytokine production, induce epithelial and goblet cell apoptosis and alter ocular surface function, perpetuating a chronic inflammatory process [2].

Inflammatory Markers

HLA-DR expression has been considered an interesting and useful measure of the ocular surface inflammation in DED activity [10]. While no or weak expression of HLA-DR is observed in impression cytology specimens of normal subjects, HLA-DR expression significantly increases in impression cytology specimens of patients with a diagnosis of Sjögren syndrome and meibomian gland disease (MGD). The strongest significant correlation with HLA-DR expression is found with corneal fluorescein staining. Significant negative relationships are also found with Schirmer's test and tear film break-up time. Correlations are also

statistically significant with the Ocular Surface Disease Index (OSDI) and visual analog scale scores [10].

MMP–9 is one key inflammatory biomarker now in clinical use. It is a proteolytic enzyme involved in the extracellular matrix remodeling that takes place after injury and has been found to be a key component of the inflammatory cycle in DED [11]. Several studies report elevated levels of MMP–9 in DED that correlate with DED severity [12, 13].

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PRACTICAL TIPS FOR IDENTIFYING INFLAMMATION IN DRY EYE DISEASE

Although inflammation is recognized as a key driving mechanism in many cases of DED, differentiating cases with a major inflammatory component from those in which inflammation plays a less fundamental role can be challenging.

The tendency to date is to address the management of inflammation in DED when in the presence of clinically apparent inflammation i.e. ocular redness. Nonetheless, the evidence suggests that most dry eyes are associated with subclinical ocular surface inflammation which may further compromise tear secretion and cause ocular surface disease and irritation symptoms even in the absence of hyperemia.

Ocular/conjunctival hyperemia

Conjunctival hyperemia is a hallmark of ocular inflammation and can be objectively evaluated by anterior segment photography using redness measurements obtained with a keratograph and/or using grading scales (e.g. Efron or Mc Monnies scale). Grading scales have shown excellent reproducibility and the keratograph redness score correlate well with subjective grading scales [14, 15]. Conjunctival hyperemia is a consistent sign of vascular dilatation and reactive change to pathological stimuli. However, it is not specific to DED and it can occur in any ocular disease with inflammation.

Corneal and conjunctival staining

Ocular surface inflammation should be assumed in patients with an unstable tear film and ocular surface epithelial disease detected by corneal and conjunctival staining with diagnostic dyes [16].

Although dry eye can occur without ocular surface damage, corneal and conjunctival dye staining scores have proven to significantly correlate with

the concentration of cytokines in tears including IFN-γ, IL-8, MIP-1α, IL-1α, IL-1β and IL-6 [17].

Prolonged tear clearance

The evaluation of tear fluid clearance from the ocular surface is a useful clue in determining the risk of inflammation for the surface of the eye. Latent cytokines and MMPs activate in the tear fluid and are susceptible to inappropriate activation when due to inadequate production and clearance of tears they are not diluted and cleared from the ocular surface. The fluorescein clearance test has shown better correlation with both irritation symptoms and corneal staining scores than the Schirmer 1 test [18, 19].

Diagnostic tests

Several biomarkers can detect subclinical inflammation and even provide information about the severity of inflammation [13] as summarized in Table 1.

Overexpression of HLA-DR has been shown in mild dry eyes without corneal and conjunctival staining and the expression pattern reflects disease progression [20].

Measuring MMP-9 activity in tears using a commercial kit can be useful to assess ocular surface subclinical inflammation in clinical practice [21]. In some cases, MMP-9 was positive in mild cases without obvious inflammation [13].

Table 1. Current tests to assess ocular inflammation in Dry Eye Disease.

Matrix metalloproteinases (MMPs)	They are secreted in tears in DED and reflect the loss of ocular surface barriers. A diagnostic device is commercially available.
Cytokine and chemokines	Their concentrations in tears reflect the level of epithelial disease. These are still experimental tests.
Ocular surface immune markers	This includes HLA-DR by impression cytology. Its expression indicates a loss of the normally immuno-suppressed environment of the ocular surface. Increased expression of HLA-DR is associated with increased DED severity.
***In vivo* confocal imaging**	IVCM can be used to show increased dendritic cell density, low sub-basal nerve density and morphological changes indicating cell maturation, subclinical inflammation and corneal nerve changes.

Ref: TFOS DEWS II Diagnostic Methodology report [22]

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MANAGEMENT OF INFLAMMATION IN DED.

TFOS- DEWS II RECOMMENDATIONS

The aim of DED management is to restore the homeostasis of the ocular surface by breaking the vicious cycle of the disease and offering long-term options to prevent a return to the vicious cycle and resurgence of symptoms [23].

A 4-step treatment algorithm was proposed considering the etiology and severity of DED as detailed in the Table below [23].

- Treatment is generally oriented by the clinical presentation. Lubricants and lid hygiene are usually first considerations in the early stages of the disease and more advanced therapies are contemplated for more severe forms.
- Anti-inflammatory therapy including short-term treatment with topical corticosteroids or topical non-glucocorticoid immunomodulatory drugs (e.g cyclosporine A [CsA], lifitegrast,) are included in step 2, when initial steps taken are not enough, along with non-preserved lubricants, de-modex management if present, tear conservation (punctal occlusion or moisture chamber spectacles), and other topical (topical secretagogues), or oral (oral macrolide or tetracycline) treatments.
- If all these previous options are still inadequate, and depending on the clinical presentation, topical corticosteroids for longer periods may be an option at later stages. However, this is still subject of debate in the ophthalmological community.

As reviewed by the TFOS-DEWS II management subcommittee [23], chronic exposure of the ocular surface to preservatives is a well-recognized cause of toxicity and adverse changes to the ocular surface [24].

Preservative-free drops, especially benzalkonium chloride (BAK)-free eye drops, are a better choice for patients who have pre-existing ocular surface conditions and/or need frequent instillation of eye drops. Preservative-free corticosteroid eye drops have shown greater effectiveness than preserved drops in decreasing inflammation on the ocular surface and increasing the antioxidant contents in tears of patients with DED [25].

Table 2. Stepwise Management algorithm of dry eye disease

Step 1
Education regarding the condition, its management, treatment and prognosis.
Modification of local environment.
Education regarding potential dietary modifications (including oral essential fatty acid supplementation.
Identification and potential modification/elimination of offending systemic and topical medications.
Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements.
Lid hygiene and warm compresses of various types.

Step 2
If above options are inadequate consider:
Non-preserved ocular lubricants to minimize preservative-induced toxicity.
Tea tree oil treatment for Demodex (if present).
Tear conservation: ▪ Punctual occlusion ▪ Moisture chamber spectades/goggles
Overnight treatments (such as ointment or moisture chamber devices).
In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow).
In-office intense pulsed light therapy for MGD.
Prescription drugs to manage DED: ▪ Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present). ▪ Topical corticosteroid (limited-duration). ▪ Topical secretagogues. ▪ Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine). ▪ Topical LFA-1 antagonist drugs (such as lifitegrast). ▪ Oral macrolide or tetracycline antibiotics.

Step 3
If above options are inadequate consider:
Oral secretagogues.
Autologous/allogeneic serum eye drops.
Therapeutic contact lens options: ▪ Soft bandage lenses ▪ Rigid scleral lenses

Step 4
If above options are inadequate consider:
Topical corticosteroid for longer duration.
Amniotic membrane grafts.
Surgical punctal occlusion.
Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation).

Ref: TFOS DEWS II Management and Therapy Report [23]

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IMPACT OF PRESERVATIVES IN THE MANAGEMENT OF INFLAMMATION IN DRY EYE DISEASE

Most of the topical corticosteroids currently on the market contain preservatives [23].

BAK is the most frequently used preservative in eye drop preparations. There are many *in vitro* and *in vivo* studies demonstrating that BAK can induce corneal and conjunctival epithelial cell apoptosis, damage the corneal nerves, delay corneal wound healing, interfere with tear film stability and cause a loss of goblet cells [23].

The toxicity of BAK is related to its concentration, the frequency of dosing, the level or amount of tear secretion and the severity of the ocular surface disease [26]. In patients with moderate-to-severe dry eye, the potential for BAK toxicity is high due to direct epithelial cell damage, on the one hand, and to decreased tear secretion and decreased turnover on the other [24].

One experimental study showed that BAK in corticosteroid formulations could decrease the anti-inflammatory effect of corticosteroids in mice and human corneal cells *in vitro* [27]. In another study, 94% of patients with severe DED recalcitrant to previous preserved corticosteroids were successfully treated with an unpreserved low-dose steroid formulation, resulting in a combined steroid anti-inflammatory effect and a lack of associated preservative toxicity [28]. In another study, preservative-free corticosteroid eye drops had greater efficacy than preserved drops in decreasing inflammation on the ocular surface and increasing the antioxidant contents in tears of patients with DED [25].

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STEROIDS IN THE MANAGEMENT OF DRY EYE DISEASE

Although artificial tears, even those supplemented with osmoprotectants (e.g. trehalose, erythritol and L-carnitine), have been shown to decrease hyperosmolarity and ocular surface inflammation, they might be not enough to address the underlying disease process [29,30]. Anti-inflammatory eye drops are thus a therapeutic option for breaking the vicious inflammatory cycle [7].

Corticosteroids are effective anti-inflammatory agents in DED and are currently indicated as a treatment option for DED by the TFOS-DEWS II in step 2 of the DEWS treatment algorithm [23] in short courses and in step 4 with longer courses. Topical corticosteroid therapy has been reported to improve both signs and symptoms of dry eye in clinical trials and is an option with a rapid onset of action.

Corticosteroids suppress both the early (capillary dilation, increased vascular permeability, recruitment of leukocytes) and late (deposition of fibrin, proliferation of inflammatory cells and chemokines) phases of inflammation [31].

Classification of Corticosteroids

Currently available corticosteroids for topical ophthalmic application include hydrocortisone, fluorometholone, loteprednol etabonate, rimexolone, prednisolone acetate, dexamethasone alcohol, dexamethasone sodium phosphate and betamethasone. They are classified according to their penetration into the anterior chamber and their effect on the intraocular pressure (IOP) into:

- **Soft corticosteroids:** hydrocortisone, fluorometholone, rimexolone, loteprednol etabonate
- **Strong corticosteroids:** dexamethasone, betamethasone, prednisolone and methyl-prednisolone.

Ideal characteristics of corticosteroids for dry eye

The ideal topical corticosteroid for DED should have:

- **Adequate potency**
  Topical applications provide high concentrations of corticosteroids at the ocular surface and, thus, there is no need for strong glucocorticoid activity in ocular surface diseases like DED. The majority of topical preparations are provided at a concentration of 0.1 to 1.0%. Very low doses of topical corticosteroids have been shown to be effective in refractory patients with chronic severe ocular surface irritation [28]. They cause fewer side effects and show greater potential for prolonged treatment if needed.

- **Low intraocular penetration**
  Low intraocular penetration is required to avoid ocular adverse events. Most topically-applied corticosteroids penetrate the eye via the cornea and reach the aqueous humour within 5 to 30 minutes after application [32]. Lipophilic acetate and alcohol preparations penetrate the cornea up to 20-fold greater than water-soluble phosphate preparations. Strong corticosteroids such as Prednisolone acetate and Dexametasone alcohol achieve high concentrations in the anterior chamber (669.9 ng/ml and 31 ng/ml respectively) compared to low intraocular concentrations reported for soft corticosteroids such as loteprednol and fluorometholone (6.25 and 5.1 ng/ml respectively) and hydrocortisone (1.5% penetration of the dose to the anterior chamber) [56]. Thus, strong corticosteroids should be chosen to treat intraocular inflammation [33], but not necessarily for the treatment of ocular surface inflammation where formulations with minimal penetration should be favored. Unsurprisingly, increased corticosteroid concentration in topical preparations generally results in higher intraocular concentrations [32].

- **Short duration of action**
  A corticosteroid with a short duration of action is preferable in avoiding adverse effects. Although the duration of action of topically-applied solutions is limited by rapid clearance through the nasolacrimal system, some topical corticosteroids are available as suspensions or ointments delivering higher drug concentrations than solutions. This may improve the therapeutic effect, but also promote intraocular penetration [33]. A corticosteroid that achieves a desired pharmacologic action followed by rapid metabolism into inactive metabolites to avoid unwanted effects is desirable [34].

- **Good safety profile**
  In addition to their therapeutic effects, topical corticosteroids can produce a number of local adverse side effects including steroid-induced IOP elevation, lower resistance to infection, risk of cataract formation and a decrease in wound healing [31, 35]. The extent of these side effects may vary significantly depending on the molecule used, the posology and patients' susceptibility [35].

- **Low systemic absorption**
  Patients who receive frequent doses of a topical steroid absorb clinically significant amounts of the drug which may result in the suppression of endogenous cortisol production which may potentially cause systemic effects [36]. Thus, topical ophthalmic corticosteroids with low systemic absorption should be considered.

- **Preservative-free formulation**
  The addition of the preservative benzalkonium chloride (BAK) to ophthalmic corticosteroid formulations has been show to possibly alter their pharmacokinetics [32]. The effect of BAK in inducing greater corticosteroid penetration is related to its known permeability enhancement effect where there is a physical disruption of epithelial cell membranes and a widening of intercellular spaces [37]. Moreover, BAK may cause or aggravate DED because of its toxic and proinflammatory effects as well as its detergent tensioactive properties [1].

Advantages of Hydrocortisone versus Other Corticosteroids

Topical hydrocortisone has some advantages compared to other corticosteroids:

Under physiological conditions, there is an autocrine synthesis of cortisol (Hydrocortisone) in corneal epithelial cells which is thought to contribute to the immune protection of the ocular surface mucosa during physiological conditions. In ocular surface diseases, toll-like receptors activation and cytokine production potently mitigate the biosynthesis of cortisol leading to a net reduction of ocular surface cortisol levels and promoting the recruitment of inflammatory cells needed to resolve the initial trigger [38].

- **Effective against dry eye inflammation**

  Hydrocortisone is a natural fast-acting corticosteroid of relative lower potency compared with synthetic corticosteroids. Clinical efficacy and safety of hydrocortisone 0.3% formulations given twice daily for 28 days have been demonstrated in clinical studies in patients with Sjögren Syndrome [39].

- **Limited anterior chamber penetration**

  In contrast to other topical corticosteroids such as dexamethasone, betamethasone, or prednisolone, the corneal penetration of hydrocortisone is limited [33; 40, 41].

- **Good safety profile**

  Its topical use as an eye drop is generally considered to have a low prevalence of ocular side effects and a good safety profile [39]. Since the intraocular penetration of hydrocortisone is low, hydrocortisone is less likely to provide high intraocular concentration and, thus, less likely to induce the intraocular adverse effects of corticosteroids [40].

Topical hydrocortisone provides a therapeutic alternative to the more potent anti-inflammatory drugs to treat ocular surface inflammation or to replace these strong corticosteroids when a patient's treatment needs to be progressively tapered.

Safety Profile and Recommended Surveillance

IOP profile

IOP elevation is a frequent adverse drug reaction of topical ophthalmic corticosteroids used over a period of weeks in both normal and glaucomatous eyes. The population can be divided into two general groups: 'steroid responders' who exhibit this response in a mild or severe form, and 'steroid non responders' in whom treatment with corticosteroids does not result in a higher IOP [32]. When treated with topical steroids for 4–6 weeks, 5% of the population demonstrates a rise in IOP greater than 16 mmHg and 30% have a rise of 6–15 mmHg [42]. Steroid responders generally constitute 18–36% of the general population. Corticosteroid effects on IOP in such patients are generally reversible [43].

Topical corticosteroids have varying effects on IOP elevation [43]. In general, the ability of a particular corticosteroid to induce elevation of IOP is proportional to several factors: the anti-inflammatory potency, the penetration to anterior chamber, the dosage of the drug and duration of treatment. Therefore, prednisolone, dexamethasone and betamethasone, which achieve higher intraocular concentrations in the anterior chamber, tend to produce corticosteroid-induced ocular hypertension more often than soft corticosteroids. In studies performed on steroid responders, strong corticosteroids such as Prednisolone have been reported to elevate IOP between 9 and 12 mmHg from baseline, dexamethasone between 11.8 to 22 mmHg compared to soft corticosteroids such as fluorometholone 3.5 to 8.4 mmHg, loteprednol 4.1 mmHg and Hydrocortisone 3.3 mmHg. The mean time to IOP elevation is significantly longer with soft corticosteroids (5.2 weeks Rimexolone and 5.4 weeks with fluorometholone) than with strong corticosteroids (2.5–3 weeks with dexamethasone and prednisolone respectively) [40,43].

This side effect is particularly observed in patients with predisposing risk factors including a personal or family history of glaucoma, pre-existing type I diabetes mellitus, and connective-tissue disease, which in turn requires diligent follow-up of these patients after receiving glucocorticoids [42].

IOP Surveillance

The typically insidious nature of corticosteroid-induced glaucoma requires careful monitoring of patients at risk to identify any early changes that would require a change in management [44]. When treatment is discontinued, the chronic

corticosteroid IOP response is typically resolved in 1–4 weeks whereas the rare acute response may be resolved within a few days of corticosteroid cessation [44].

Cataract risk

Cataract formation, especially in the form of posterior subcapsular lens opacities, is a widely known complication of corticosteroid therapy with an incidence of 22–58% [31; 35,54]. Osmotic imbalance, oxidative damage, an imbalance of growth factors and subsequent levels in cellular enzymatic levels and upregulation of MMP activity probably play prominent roles in cataract genesis [55]. Soft corticosteroids have been shown to be less cataractogenic [35].

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ADDITIONAL OPTIONS FOR THE MANAGEMENT OF INFLAMMATION IN DRY EYE DISEASE

Immunomodulatory Antibiotics

Tetracyclines and derivatives (minocycline, doxycycline) decrease the bacterial load and exert anti-inflammatory and antiangiogenic effects. Given these actions, they are especially beneficial in EDE patients with rosacea and blepharitis [45].

They act by inhibiting bacterial flora which produces lipolytic exoenzymes and lipase enzymes. They decrease collagenase activity, phospholipase A2 and matrix MMPs activities in addition to inhibiting IL-1 and TNF-α production in corneal epithelium and ocular surface structures. Oral tetracycline can be used 250 mg 4 times daily or as doxycycline 40–100 mg/d or minocycline 50 mg/d. Generally, the effect of the treatment is observed after 6–8 weeks or even longer in some patients [45].

Azithromycin can be a valuable option when MGD occurs in association with rosacea [23], and the anti-inflammatory properties are believed to possibly help control bacterial flora and lid inflammation. Several clinical studies support the efficacy and safety of oral or topical azithromycin in the management of DED, especially in patients with severe blepharitis [23]. Topical azithromycin has been shown to have the same efficacy as oral doxycycline in the treatment of MGD [46].

Autologous Serum and other Blood Derivatives

Many studies have reported that autologous serum eye drops are effective for the treatment of ocular surface diseases including superior limbic keratoconjunctivitis, recurrent corneal erosions, neurotrophic keratopathy, persistent epithelial defects and Sjogren's syndrome [47]. However, their widespread use is limited by a number of logistic factors such as preparation, storage, administration, legal demands and cost [23, 48].

Autologous serums contain a number of anti-inflammatory factors that have the potential to inhibit soluble mediators of the ocular surface inflammatory cascade of dry eye. These include inhibitors of inflammatory cytokines (for example, IL-1RA and soluble TNF-α receptors) and matrix metalloproteinase inhibitors (for example, tissue inhibitors of metalloproteinases [TIMPs]). Autologous serum drops have been reported to improve ocular irritation symptoms and conjunctival and corneal dye staining in several clinical studies, predominantly in patients with severe DED due to Sjögren syndrome [23].

Similarly, plasma rich in growth factors can improve symptoms and reduce corneal staining in DED patients [23].

Cyclosporine A

Topical cyclosporine 0.05% was approved in 2003 by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe DED and topical cyclosporine A 0.1% by the European Medicines Agency (EMA) in 2015 for the treatment of severe keratitis in adult patients with DED that has not improved despite the use of tear substitutes. Treatment with cyclosporine reduces many markers of inflammation, reduces elevated tear osmolarity and increases tear secretion as assessed by the Schirmer test. Additionally, cyclosporine treatment has been reported to result in the recovery of reduced goblet cell density in the conjunctiva of subjects with DED [23]. The action of topical CsA is progressive as 6-8 weeks of application is typically needed in most patients before demonstrable efficacy is observed. It can be adapted for long-term management of the ocular surface, after a first pulse therapy with topical corticosteroids [49].

Other Therapeutic Options

Lifitegrast is an inhibitor of the adhesion, migration, activation and recruitment of T cells because it blocks LFA-1/ICAM-1 interaction [23]. The efficacy and safety of the Lifitegrast 5% ophthalmic solution has been established in randomized controlled clinical trials in patients with DED.

Other options include dietary modifications such as omega-3 essential fatty acids and antioxidant oral supplementation [23].

8

PEARLS IN MANAGING INFLAMMATION IN DRY EYE DISEASE

Management of Acute Exacerbations

- Environmental desiccating conditions can result in sudden episodes of worsening ocular symptoms in DED patients. The treatment of these acute exacerbations should target the increased inflammatory activity [50, 51].
- A topical soft steroid therapy (4 drops daily, tapered over 2-4 weeks) may be a suitable approach for DED patients who experience exacerbations under desiccating conditions in their daily life and do not improve [52,53].

Management of Chronic Inflammation in Dry Eye Disease

Mild cases:

- Because available diagnostic methods are not able to quantify the level of inflammation, no firm recommendations can be made regarding the optimal timing for initiating anti-inflammatory therapy in patients with dry eye [16].
- Treatment with soft topical corticosteroids may be a second line therapy in mild to moderate DED when artificial tears are not enough [49].
- The optimal minimum concentration of corticosteroids for minor ocular inflammatory conditions has not been determined.

Moderate to severe cases:

- As suggested in the literature [49], in patients with moderate to severe dry eye, a short-term pretreatment (one drop twice daily) for 2 weeks with topical corticosteroids may be used as induction therapy for chronic medications

such as CsA [7]. This approach has proven to provide more rapid relief of dry eye signs and symptoms with greater efficacy than CsA and artificial tears alone [49].

- For long-term treatment of severe cases, a pulse therapy consisting of treatment with topical corticosteroids 4 times per day followed by reevaluation every 2 weeks on which it was decided either to taper or repeat treatment until treatment had been suspended resulted in the improvement of ocular signs for several weeks to months with only 20% recurrence while minimizing the risk of adverse events [6, 52]. Repeated short-term pulse therapy was appropriate and produced a disease-free state for more than 1 year in a study of patients with Sjögren's syndrome [52]. Topical non-preserved therapy was proven to be a safe, effective long-term treatment for subjective and objective dry eye factors in DED patients with Sjögren's syndrome [52].
- Severe inflammation should be treated aggressively (at least every 4–6 hours) until clinical evidence of improvement is seen. The frequency of application should then be gradually tapered to decrease the possibility of recurrence and to diminish side effects [33].
- The use of preservative-free formulations is advisable as BAK and preservatives may increase the corneal penetration of topical corticosteroids and promote ocular surface inflammation when used in the long term.
- Short courses of topical corticosteroids are also an important option for patients exacerbating under the use of cyclosporine 0.1% eye drops.

PRACTICAL MANAGEMENT OF INFLAMMATION IN DRY EYE

There is no easy method for detecting inflammation in dry eye. Clinical signs such as hyperemia or corneal and conjunctival staining point to the presence of inflammation but their absence does not rule it out. Inflammation must be presumed present when basic dry eye treatment measures are not proving to be as effective as would be expected. Treatment of inflammation should begin as soon as possible to interrupt and avoid the perpetuation of the inflammatory dry eye cycle and possibly avoid the progression of the disease. The ideal first option for short-term management of inflammation in dry eye is a soft, preservative-free corticosteroid.

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