International Journal of Enhanced Research in Educational Development (IJERED)
ISSN: 2320-8708, Vol. 11 Issue 1, Jan-Feb, 2023, Impact Factor: 7.326

A Review on Dry Eye Syndrome: Use of Corticosteroid Loteprednol etabonate in Ophthalmic Formulation

Akash Bhagat[1], Jitendra Shinde[2], Bhushan Borole[3], Ajay Khopade[4]
Vaishnav Kulkarni[5]

[*1,5]M pharm Department of Pharmaceutics, PDEA's Seth Govind Raghunath sable College of Pharmacy, Purandhar (Saswad), Pune, Maharashtra 412301
[2]HOD Department of Pharmaceutics, PDEA's Seth Govind Raghunath sable College of Pharmacy, Purandhar (Saswad), Pune, Maharashtra 412301
[3]Manager of Formulation Research & Development of Non Oral Department, Sun Pharmaceutical Industries Ltd., R&D Centre, Vadodara, 390020, Gujarat, India
[4]Vice President ofFormulation Research & Development of Non Oral Department, Sun Pharmaceutical Industries Ltd., R&D Centre, Vadodara, 390020, Gujarat, India

ABSTRACT

Millions of people worldwide suffer from dry eye disease, a common ocular condition. This review provides in-depth information about dry eye disease prevalence, definition, causes, diagnostic tests, and medical treatment & use of corticosteroid. Ocular surface diseases like dry eye disease (DED) are very common. Patients with DED may experience sporadic flares, just as they do with any other chronic disease. There are numerous current and upcoming treatments for the chronic treatment of DED; however, there are few treatments for DED flares. For ocular inflammation, corticosteroids are an important treatment option. But clinicians still worry about safety, especially when used for a long time. Topical ophthalmic corticosteroids are highly effective at suppressing allergic and inflammatory responses, but there is a risk of side effects like elevated intraocular pressure (IOP), which can lead to glaucoma. Since the C-20 position of the corticosteroid loteprednol etabonate (LE) is occupied by an ester rather than a ketone, the risk of adverse effects like elevation of IOP is minimized. Loteprednol etabonate 0.25% is a treatment method approved by the FDA for the temporary treatment of DED symptoms and side effects. This medication is formulated with specialised mucus-penetrating particle (MPP) technology, which has a greater capacity to penetrate the ocular surface and delivers the active steroid to the ocular surface tissues more effectively than conventional steroid preparations. Loteprednol etabonate 0.25% is also being used more and more to treat DED before, during, or after cataract or refractive surgery. It can also be used to start a long-term immunomodulatory treatment for DED as an induction therapy.

Key Words: Corticosteroids, dry eye disease (DED), intraocular pressure (IOP), loteprednol etabonate 0.25% (LE), mucus-penetrating particle technology (MPP).

INTRODUCTION

Reduced tear production or excessive tear evaporation, which harms the interpalpebral ocular surface, is the cause of dry eye disease, a tear film problem. It is a multifactorial condition that affects the tear film and ocular surface and causes discomfort, visual disturbances, and tears film instability, in addition to the possibility of ocular surface injury. The ocular surface is inflamed, and the tear film's osmolality is elevated in addition to this. [1]

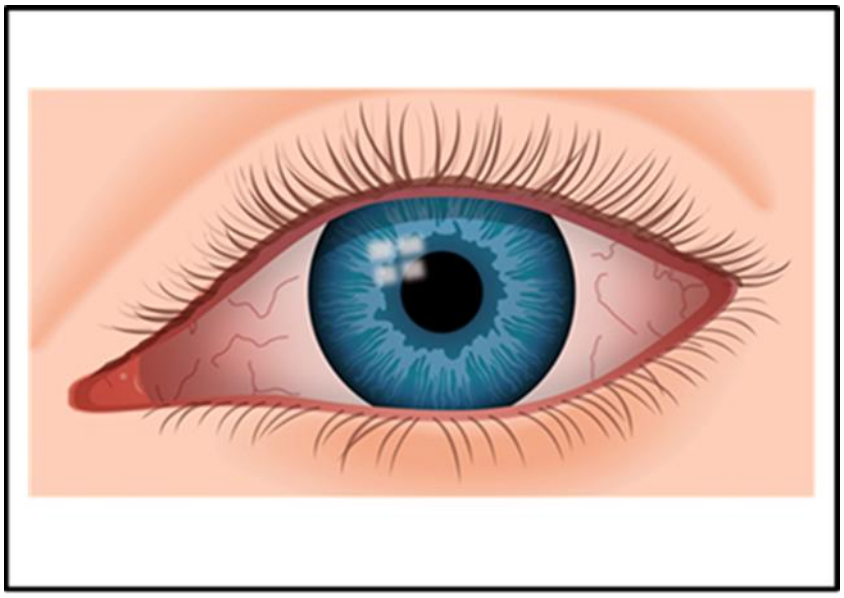

Figure 1: Dry Eye Syndrome

In people with dry eyes, significant ocular surface damage may develop. [2] Because it makes it difficult for them to perform daily tasks like using the stairs, identifying friends, reading, watching TV, working on a computer, or driving, especially at night, it is damaging to their quality of life. [3] Xerophthalmia, dry eye disease (DED), ocular surface disease (OSD), dysfunctional tear syndrome (DTS), keratoconjunctivitis sicca (KCS), keratitis sicca, sicca syndrome, and plain dry eyes are other names for dry eye syndrome (DES). [4] Millions of people worldwide suffer from dry eye, which affects anywhere from 5 percentage to 35 percentage of the population. [5]

PREVALENCE OF DRY EYE SYNDROME

As people get older, the prevalence of dry eye syndrome goes up. DES is a common eye disorder that affects a significant number of people, particularly those who are over the age of 50. [6, 7] Due to the high prevalence of contact lens use, systemic drug effects, autoimmune diseases, and refractive surgeries in these age groups, middle-aged and older adults are the most frequently affected. [8, 9] Between 25 and 30 million people worldwide are thought to be affected by DES. In addition, research reveals that DES can affect people of any race and is more prevalent in women than in men. [10, 11] An imbalance occurs in the hormones oestrogen and androgen in women between the ages of 50 and 52, when menopause typically begins. The normal homeostatic maintenance of the lacrimal gland and ocular surface is disrupted as a result of this stimulating inflammation. KCS is present in up to 20% of people with rheumatoid arthritis. [11, 12] Patients with Helicobacter pylori, computer users, and people who wear contact lenses for a long time are also likely to be affected. [13, 14]

CAUSES FOR DRY EYE SYNDROME

Reduced tear production, increased tear evaporation, and abnormalities in the synthesis of mucus or lipids in the tear layer are all contributing factors to DES. [15, 16, 17] People with autoimmune disorders, including primary Sjögren's syndrome and rheumatoid arthritis, as well as older patients, postmenopausal women, and patients with these conditions, are more likely to experience dry eyes with inadequate tear production. [18, 19, 20] Changes in the tear film's stability and composition brought on by lacrimal functional unit dysfunction result in ocular surface irritation. [21, 22, 23] Aqueous tear deficit (ATD) and dry mouth are two features of Sjogren's syndrome (SS). [24] Lymphocytes gradually infiltrate the lacrimal and salivary glands in every case of SS, disrupting the normal structure of the glands and resulting in their loss of function. [25, 26]

Patients with non-Sjogren's disorder have infections of the tear organ such as trachoma, sarcoidosis, and lymphoma.[27] In instances of evaporative dry eyes, eyes dry out on account of more prominent tear dissipation, as in instances of decreased squinting and top surface oddities. Ecological factors, for example, focal warming, a dry environment, air contamination, wind, compound consumption, contact focal point wear, or diminished flickering due to driving, staring at the television, and PC work can influence the tear film and lead to disease, a corneal ulcer, and visual deficiency. [28, 29, 30] Rosacea, blepharitis, and MGD (meibomian organ brokenness) are significant reasons for evaporative dry eyes. Because of meibomian organ breakdown caused by rosacea, there is unusual production of lipid[31]

SYMPTOMS FOR DRY EYE SYNDROME

A dry, gritty feeling in the eyes is the predominant sign of dry eyes. Additional signs and symptoms include eye pain and redness; excessive tearing; burning or itching in the eyes; and, in certain cases, photophobia. [32, 33] Your vision may change, and occasionally you may also have a stringy discharge. In dry conditions with low humidity and greater temperatures, it has been seen that symptoms deteriorate. [34]

DIAGNOSIS

Diagnostic tests are required to distinguish between dry eye, infections, and allergies, which can present clinically very similarly but require distinct treatments. Dry eye may get worse if an incorrect clinical diagnosis is made and antiallergic medications or epitheliotoxic antibiotics are given. Patients can be placed into one of two treatment-based subgroups using the diagnostic tests: "hyper evaporative" or "aqueous-deficient." [35]

Examination of the eyelids

Blink rate

Blinking encourages meibomian gland secretion and helps distribute tear fluid across the ocular surface. While speaking, the typical blink rate ranges from 15.5 to 13.7 blinks per minute. The blink rate decreases significantly from 5.3 to 4.5 blinks per minute while reading and working on a computer, facilitating the evaporation of tear fluid. Dry eye patients typically have incomplete blinking and a reduced blink interval of approximately 2.6 seconds. [36]

Lid margin

An in-depth examination of the eyelid margin will reveal any inflammation or meibomian gland dysfunction associated with hyper evaporative disorder. The slit lamp is used to examine the eyelashes, margins of the eyelid, and orifices of the meibomian gland.

Lid congruity and lid closure

The integrity of the tear film on the ocular surface can be disrupted by lid incongruity (e.g., ectropion, entropion) or insufficient lid closure (e.g., facial nerve palsy), both of which require surgical correction. [37]

Examination of the conjunctiva

In straight gaze, the lid-conjunctiva friction results in temporal lid-parallel conjunctival folds (LIPCOFs). With a sensitivity of 84.9% and a specificity of up to 90%, they are considered an important indicator of dry eye. The slit lamp makes it easy, quick, and non-invasive to identify them. [38]

Examination of the ocular surface

The slit lamp and vital stains are used to examine the eye's surface. In clinical practice, fluorescein and lissamine green are the most common dyes. The precorneal tear film as well as epithelial erosions in the conjunctiva and cornea is stained with fluorescein. The mucin layer of cells with superficial damage is highlighted by lissamine green. [39]

Examination of the tear film

Tear film meniscus

During a slit-lamp examination, the height of the tear film meniscus can be measured, which can indicate the presence of hypo secretory dry eye. Optical coherence tomography can be used to objectively measure the tear film. [40]

Tear Film Breakup Time (TBUT)

TBUT is the amount of time it takes for the tear film to separate after a blink. It is a quantitative test to determine the stability of the tear film. [41] Breaking up a tear film typically takes 15 to 20 seconds. The inferior cul-de-sac is treated with saline and a fluorescein strip. A broad-beam slit lamp with a blue filter is used to look for the first dry spots on the cornea in the tear film after several blinks. Patients who suffer from mild to moderate dry eye disease typically have TBUT values that are less than 5–10 seconds, which indicates tear instability. [42]

Schirmer Test

The Schirmer test quantifies the amount of tears produced by the lacrimal gland over a predetermined time frame. [43] Putting a thin strip of filter paper in the lower cul-de-sac after administering topical anaesthesia is the fundamental test. [44, 45] The length of the wet strip is used to measure the amount of tears that wet the paper after the patient's eyes are closed for five minutes. By stimulating the lacrimal reflex arc, this Schirmer II test measures the lacrimal gland tear, and 15 mm of wetting after five minutes is considered abnormal. [46]

Tear Osmolarity
The normal osmolarity of the eye is 309–312 mOsm/L, and the value rises as dry eye disease progresses. It provides qualitative data regarding tear production. Although it lacks specificity, this test is very sensitive. In Lemp et al., in a multicentre study, when compared to other tests like the TBUT, staining, Schirmer test, and meibomian gland grading, it was determined that the tear osmolarity test was the most effective single method for diagnosing and determining the severity of DES. [47]

Tear Function Index (TFI)
It is a quantitative tear measurement test that is more specific and sensitive. It helps identify subjects with dry eye and evaluates the tear production and drainage dynamics. By dividing the Schirmer II test value in millimetres by the tear clearance rate; its numerical value is determined. The ocular surface is better when the numerical value of TFI is higher. Anything below 96 indicates dry eyes. [48]

Tear Fluid Protein Immunoassays
Using enzyme-linked immunosorbent assay (ELISA) methods, tear lysozyme, tear lactoferrin, epidermal growth factor (EGF), aquaporin 5, lipocalin, and immunoglobulin A (IgA) concentrations, in addition to tear-film osmolarity, can be used to measure the protein content of tears. [49, 50]

Tear Ferning Test (TFT)
The tear ferning test (TFT) can be used to diagnose hyperosmolarity, mucin, DES, and the quality of the tears. A drop of tear fluid is taken from the lower eyelid, placed on a microscope slide, and left to evaporate before being examined. Branching crystallisation patterns of various types are observed and categorized. Based on the patterns of ferning, the test determines dry eyes. [51]

Symptom Questionnaires
Different aspects of dry eye disease, such as diagnosis, precipitation factors, and impact on quality of life, are examined in depth by questionnaires. [52] A structured questionnaire given to patients assists clinicians in screening patients for dry eye disease. A specific questionnaire can be selected depending on the intended use of data, for example, for diagnosis use only, for recruiting patients to a clinical trial, or for treatment. [53]

Other Tests
Meibometry, meibography, and meiboscopy are three procedures used to identify meibomian gland dysfunction (MGD). Evaporimetry is used to measure tear evaporation. Dry eyes can be diagnosed with an aqueous-rear deficit by meniscometry. For the diagnosis of Sjogren's syndrome, a lacrimal gland or minor (salivary) gland biopsy may be performed. [54]

MEDICAL TREATMENT OF DRY EYE

There are numerous keratoconjunctivitis therapies available. Relieving dry eye symptoms, enhancing patient comfort, restoring the ocular surface and tear film to their pre-dry eye conditions, and, whenever possible, preventing corneal damage are the objectives of treatment.

Corticosteroids
It has been discovered that topical corticosteroids, including loteprednol etabonate, dexamethasone, prednisolone, and fluorometholone, are useful in treating inflammatory diseases linked to KCS. The FDA has approved these medications for treating inflammatory conditions of the conjunctiva, cornea, and anterior globe. They are often advised for short-term usage because continued use might have negative effects such as glaucoma, cataracts, and eye infections. [55, 56, 57]

Artificial tears
Lubricant eye drops called artificial tears are used to relieve the dryness and discomfort brought on by KCS patients' inadequate tear production. The first line of treatment is typically lubricating tears, which are sold over-the-counter. Lubricant drops must be applied four times per day for mild illness conditions, and more frequently (10-12 times per day) for severe disorders. These OTC products differ mostly in terms of their contents, indications, and preservative availability. Their viscosity, retention period, and level of adherence to the ocular surface are influenced by ingredients such as cellulose and polyvinyl derivatives, chondroitin sulphate, and sodium hyaluronate. [58]

Autologous Serum Eye Drops
The several vital tear components found in autologous serum eye drops, including fibronectin, vitamin A, hepatocyte growth factor, and epidermal growth factor, are crucial for maintaining a healthy ocular surface. [59]

Nonsteroidal Anti-Inflammatory Drugs and Antibiotics
NSAID drops that comprise diclofenac sodium and ketorolac lessen the inflammation brought on by DES. Meibomian gland dysfunction is treated with ophthalmic ointments that contain antibiotics like erythromycin and bacitracin. [60]

Punctal Plugs
In order to prevent nasolacrimal drainage of tears from the eye and dry eyes, a small medical device known as a "punctal plug" is inserted into the puncta of an eye. Clinical studies have demonstrated that punctal plugs improve DED symptoms and signs as an occlusion method.

Immunosuppressive agents
Numerous ocular immune pathologies can be effectively treated with cyclosporine A. Local ophthalmic conditions involving cytokines, such as corneal graft rejection, autoimmune uveitis, and dry eye syndrome, are treated with systemic administration of the drug. However, it causes severe cardiovascular and renal problems. [61]

Vitamin A
The tear film of healthy eyes naturally contains vitamin A, an essential nutrient. [62] The mucin layer, the tear film's innermost lubricating layer, is made in large part by vitamin A, which is necessary for a healthy tear film. Goblet cell atrophy and the loss of the mucin layer are both caused by vitamin A deficiency. Eyes are shielded from free radicals, toxins, allergens, inflammation, and vitamin A drops. KCS treatment options have included systemic vitamin A administration and topical retinoic acid therapy. [63, 64]

Omega 3 Fatty Acids
Ophthalmologists today recommend taking arachidonic acid and essential fatty acids orally. Eicosanoids are the precursors of EFAs, which are hormones that act locally and play a role in regulating inflammatory processes. Patients with DED may benefit from essential fatty acids by altering the composition of meibomian lipids and lowering inflammation. Dietary changes containing n-3 fatty acids may be suggested by doctors to alleviate DES symptoms. [65, 66]

CURRENT CHALLENGES AND FUTURE ASPECTS

The most frequent ophthalmic symptom is dry eye syndrome, which, if left untreated, increases the risk of corneal ulcers, eye infections, and blindness. Due to the wide range of signs and symptoms as well as the lack of clarity regarding the aetiology and pathophysiology of the disease, the clinical diagnosis of dry eye is difficult. Uncertain symptoms could lead a doctor to mistakenly treat a patient for another ailment, such as conjunctivochalasis, which easily produces an unstable tear film (which is a frequent cause of ocular irritation). [67] The Schirmer test, TBUT, and ocular staining are examples of conventional methods for diagnosis; as was already said, some of them have a low level of standardisation and some are invasive. Some diagnostic tests are intrusive, which might make interpretation difficult. A "tear film" is a dynamic, open system that is subject to a wide range of internal and external fluctuations, which might cause errors in the interpretation of the results. [68]

According to recent studies, less than 60% of patients with additional objective signs of DED are symptomatic. [69] Therefore, relying just on symptoms will lead to a major underrepresentation of DED patients. Osmolarity has been demonstrated to be the best single clinical indicator for identifying dry eyes, and it is directly correlated with the severity of the condition. The subtype of the disease is identified through clinical examination and other evaluations. In conclusion, reliable testing and differential diagnosis of dry eye, which are essential for the medical management of the condition, are challenging, and ophthalmologists have used the findings of numerous tests assessing tear volume and biological components to precisely identify KCS. As a result, clinicians have a hard job when it comes to identifying dry eye symptoms, choosing the best diagnostic tools and products, interpreting the results, and educating patients on how to take their medications. [70, 71]

With sales of more than $20 billion, ophthalmic medications represent a significant portion of the global pharmaceutical market. As a result, an increasing number of pharmaceutical firms are concentrating on creating novel medications for DED that can reduce inflammation or activate the production of mucin and tears. The symptoms and outward manifestations of DED are reduced by current treatments such as lubricants and anti-inflammatory medications, but the disease's underlying cause is still unaddressed. There are numerous medications being developed, as well as various preclinical and clinical research pipelines for current medications. [72, 73]

The current regimen focuses on using topically applied artificial tears, controlling tear retention, enhancing tear production, and anti-inflammatory medications. Future successful management of dry eyes, or keratoconjunctivitis sicca, will depend on new therapeutic approaches, novel drug delivery systems, and the incorporation of improved

endpoints for clinical trials. These approaches will use pharmaceutical compounds designed to inhibit key inflammatory pathways and restore a healthy tear film. [74, 75]

ROLE OFCORTICOSTEROIDS IN TREATMENT OF DES

Often, the initial step in the treatment of DED is ocular lubrication. More symptomatic DED patients frequently need additional treatment modalities, even though they are still regarded as a mainstay of therapy. Prior to this, the only way to treat DED with topical corticosteroids was off-label. The effectiveness of topical corticosteroids in the treatment of DED patients has been supported by numerous clinical investigations. [76]

It is believed that topical corticosteroids, which are potent anti-inflammatory drugs, can aid in stopping the cycle of inflammation in DED. Topical steroids have been found in animal models to greatly lower MAPK signalling pathway activity and MMP-9 production, both of which have been linked to the aetiology of DED. [77] Additionally, steroids reduce the expression of cell adhesion molecules like ICAM-1 and suppress the production of inflammatory cytokines and chemokines like IL-1, IL-6, and TNF-alpha, all of which are involved in the inflammatory pathophysiology of DED. [77] However, prolonged use of topical corticosteroids has been linked to a number of ocular side effects, including the development of cataracts and glaucoma and an elevated risk of infection. [78]

LOTEPREDNOL ETABONATE

In loteprednol etabonate, the ketone at the carbon-20 position is substituted by a cleavable 17B-chloromethyl ester, resulting in the active steroid being formed. [78] It is rapidly de-esterified into inactive metabolites after exerting its therapeutic effects. [79] As a result, both short-term and long-term use shows fewer side effects, such as clinically significant intraocular pressure (IOP) elevations. [80]

Several studies have investigated the usefulness of loteprednol etabonate. The treatment of DED with loteprednol etabonate has been shown to improve the signs and symptoms of DED as monotherapy or incombination with artificial tears and cyclosporine at a concentration of 0.5%, particularly in the presence of an inflammatory component. [80, 81, 82]

Since 1998, the FDA has approved LE in two ophthalmic formulations: 0.2% ophthalmic suspension for the temporary relief of symptoms associated with seasonal allergic conjunctivitis and 0.5% ophthalmic suspension for the treatment of postoperative inflammation and pain following ocular surgery. LE 0.5% ophthalmic gel, LE 0.5% ophthalmic ointment, and LE 0.5% combined with tobramycin 0.3% ophthalmic suspension are now commercially available in the United States.[80, 81, 82]

HOW DOES LOTEPREDNOL ETABONATE 0.25% WORK AND WHAT IS THE MUCUS-PENETRATING PARTICLE (MPP) TECHNOLOGY?

Due to anatomic and physiologic barriers that normally protect the eye and have a negative impact on the bioavailability of these topical formulations, it can be difficult to deliver topical medications to the tissues of the anterior segment. These barriers can be dynamic, like conjunctival blood and lymphatic flow and tear film, or static, like the corneal and conjunctival epithelium and stroma. [83]

Drugs can travel through the conjunctival lymphatic and blood circulation systems. Hydrophilic mucin, which is found in the tear film and has the ability to capture and remove topical medication formulations from the ocular surface, is also secreted by the conjunctiva. The cornea has a hydrophilic stroma and a hydrophobic epithelium, which prevent the passage of either overly hydrophilic or hydrophobic substances. Efflux pumps can be found in the conjunctiva and cornea as well. Less than 5% of the applied dose is available for absorption thanks to the tear film, which has a quick restoration period of two to three minutes and may wash away the majority of topically applied solutions within 15 to 30 seconds after instillation. [83, 84]

The capacity of nanoparticles to enter the eye surface may still be hindered by the sticky ocular mucus layer, but advancements in drug delivery technology like nanoparticles may have the potential to improve ocular tissue penetration. Normally, a protective layer is formed by the viscous, adhesive mucus layer, which is mostly made up of cross linked and entangled mucin fibres and traps and eliminates foreign particles. Nanoparticles need to be small enough to avoid steric hindrance by the dense fibre mesh and have surface characteristics like hydrophilicity and a neutral charge to prevent adherence in order to flow through mucus. [85] Engineering nanoparticles with mucus-penetrating properties (MPPs) prevents mucins from encasing medication particles by penetrating mucus effectively. These nanoparticles have a thick layer of low-molecular-weight polymer covering them. [86]

Drug-core MPPs, which were recently developed using MPP technology, do not require that the pharmaceuticals be encapsulated in a polymeric matrix and instead are made entirely of the drugs with nanometer-scale particle size and a coating that resists adhesion to mucins. Drug-core MPPs are also stable in ready to use aqueous suspensions, such as aqueous suspension eye drops, and can be kept at room temperature. [87]

Schopf et al have led preclinical examinations exploring visual conveyance of effective loteprednol etabonate planned as MPPs. [88, 89]

Schopf et al. used a formulation of loteprednol etabonate-MPP and discovered that, when compared to rabbits receiving topical administration of conventional loteprednol etabonate, there was a 3.6-fold increase in maximum drug concentration at the cornea, a 1.5-fold increase in total drug availability at the cornea, and a 2.6-fold increase in total drug availability at the conjunctiva. These experiments showed that although the quantity of the drug was lower in the MPP formulation, loteprednol etabonate manufactured using MMP technology had a stronger ability to penetrate the ocular surface and more efficiently transport the active steroid to the ocular surface tissues. [89]

LOTEPREDNOL ETABONATE MARKETED FORMULATION WITH MUCUS-PENETRATING PARTICLE (MPP) TECHNOLOGY

The Food and Drug Administration (FDA) initially authorised KPI-121 (EYSUVIS, Kala Pharmaceuticals, Inc.) in 2019 for the treatment of postoperative inflammation and discomfort after ocular surgery, but at a concentration of 1%. Because it exhibited a better pharmacokinetic profile at the lower dose strength compared to that of traditional loteprednol etabonate suspension (0.5% without the MPP drug delivery technology), the 0.25% concentration was researched and chosen for the treatment of DED. [90]

THE ROLE OF LOTEPREDNOL ETABONATE 0.25% IN THE TREATMENT OF DED

DED patients who experience recurrent flares of the disease despite receiving long-term treatment are a common occurrence for clinicians. DED flares are characterized by episodes of increasing ocular surface discomfort and an increase in ocular surface inflammation, keratopathy, or tear deficiency on clinical examination. This may occur several times per year after the initial DED treatment. [91]

KP-121 0.25 % therapy is a great addition for patients who present with a DED flare.Because of its favourable pharmacologic profile, loteprednol etabonate can be delivered to the ocular surface in high concentration and broken down quickly, reducing adverse effects like cataract formation and elevated intraocular pressure. During a DED flare, KP-121 0.25% should be given four times a day for two weeks to break the cycle of ocular surface inflammation and alleviate the patient's acute symptoms. Most patients have flares once or twice a year, and KP-121 0.25% can be used safely during these episodes. However, it is essential to recognise that a patient's underlying DED is poorly controlled if flares occur frequently. Therefore, in order to lessen the severity and frequency of episodic flares, their baseline DED therapy needs to be modified or enhanced. [91]

Similar to this, significant ocular surface disease can also be treated prior to surgery with 0.25% KP-121. KPI-121 0.25% can be used in place of conventional topical ophthalmic corticosteroids to improve the ocular surface prior to cataract or refractive surgery. In order to ensure that patients have excellent visual outcomes following surgery, obtaining biometric measurements for intraocular lens power calculations and refractions for refractive surgery treatment planning necessitate a stable ocular surface. Similar to cataract or refractive surgery, ocular surface disease can worsen after surgery, particularly if it is not adequately treated before the procedure. Before and after surgery, 0.25% KP-121 can be used to treat DED for a short time. [91, 92]

Last but not least, KP-121 0.25% can be used as an immunomodulatory therapy induction in DED. When a patient begins effective immunomodulatory treatment, which typically takes four to about a month and a half, KPI-121, 0.25%, can be used for quite some time to mitigate side effects of DED and visual surface irritation. [92]

CONCLUSION

The extensive complexity of dry eye illness makes accurate diagnosis and management difficult. Recent understanding of DED's diagnostic tests, causes, and symptoms offers better chances for enhancing medical care. Loteprednol etabonate can be delivered to the ocular surface effectively and efficiently with little risk of side effects using KP-121 0.25%, a medication with custom-engineered MPP technology. Clinical trials have shown this drug's effectiveness in treating DED flare-ups; therefore, doctors should add it to their toolbox for treating DED.

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