Although not vision-threatening, seasonal allergic conjunctivitis accounts for a significant amount of patient morbidity, discomfort, and cosmetic concern.

The antigens associated with seasonal allergic conjunctivitis tend to originate from pollens. Depending on the geographical location and the patient’s atopic condition, these ocular allergies can occur seasonally, last year round, or recur frequently throughout the year.

In response to re-exposure to a specific antigen, the sensitised mast cells found in abundance in the conjunctiva degranulate and release histamine and other inflammatory chemical mediators. This process promotes vasodilation, edema, and recruitment of eosinophils, which further stimulates and propagates the allergic response.

Patients suffer classic symptoms of itching, eyelid swelling, burning, stinging, conjunctival hyperemia, chemosis, and mucoid or watery discharge. Attacks are usually short-lived and episodic but can be longer and often recur frequently depending on the allergen and the patient’s susceptibility to it.

A variety of over-the-counter and prescription ophthalmic pharmaceutical preparations are available for the treatment of allergic conjunctivitis. Complete avoidance of allergen exposure may be difficult for many patients. Cold compresses can offer temporary relief. Artificial tears have a dual effect by lubricating the irritated allergic ocular surface and washing away the potential pathogenic allergens from the ocular surface.

Topical vasoconstrictors with or without antihistamines may provide acute relief, but when used for more than 5-7 days, they may predispose a patient to a possible rebound phenomenon of symptoms when the medication is abruptly discontinued.

Topical ophthalmic antihistamines have a significant role in treatment. As histamine H1-receptor blockers, they reduce the symptoms of itching, but alone do not take care of the erythema associated with the H2-receptor stimulation. Pure mast cell stabilisers are effective, but they are primarily used for prophylaxis and control of chronic allergic conditions. Stabilising the mast cell membrane helps diminish the release of many of the inflammatory chemical mediators. The newest class of ophthalmic anti-allergy drug contains a combination of a mast cell stabiliser and an antihistamine. These offer immediate relief of acute symptoms because of their blockade of the histamine H1 receptors and their ability to reduce the release of many of the other inflammatory chemical mediators. Topical non-steroidal anti-inflammatory drugs have their effect at only one portion of the inflammatory cascade (the blockade of cyclooxygenase and the production of prostaglandins and lipooxygenase products) and therefore offer relatively limited benefit to patients with allergic eye disease.

**Figure 1:** Exposure to an allergen leads to an inflammatory cascade.
of the prostanoids from arachidonic acid). These drugs offer no advantages related to the reduction of the other chemical mediators of inflammation (histamine, platelet activation factor, leukotrienes).

Topical ophthalmic steroids have the potential to block, reduce, or inhibit the production of virtually all inflammatory chemical mediators found along the inflammatory cascade. Nearly all mammalian cells have steroid receptors.

Steroids modulate gene expression in the cell nucleus by inhibiting the transcription of DNA and downregulating inflammation. Although steroids do not block histamine receptors as antihistamines do, steroids inhibit the synthesis of histamine in mast cells by blocking the action of the pyruvyl-containing enzyme, histidine decarboxylase. Steroids also deplete the available (unbound) histamine, the principal mediator of the allergic ocular response, by increasing the stores of histaminase, a copper enzyme that catalyses the metabolism of free histamine into an inactive metabolite. Steroids have significant effects on inflammation at a cellular level by stabilising intracellular and extracellular membranes.

They inhibit the degranulation of mast cells, basophils, and neutrophils. Steroids suppress lymphocyte proliferation, reduce capillary permeability, and therefore reduce cellular infiltrates.

Steroids inhibit the synthesis of phospholipase A, which produces arachidonic acid from the phospholipids found in the cell wall. Arachidonic acid is the main biochemical precursor of the potent inflammatory chemical mediators: the eicosanoids (e.g., leukotrienes) and the prostanoids (e.g., prostaglandins).

With such a broad spectrum of anti-inflammatory properties, steroids have the potential to relieve nearly all signs and symptoms associated with the ocular allergic response.

Systemic steroids have been used by non-ophthalmologists for the treatment of acute and chronic systemic inflammatory and allergic reactions. Topical ophthalmic steroids are frequently the drugs of first choice for internal ocular inflammation; however, they are often the drugs of last choice for external ocular inflammation.

The use of topical steroids as a first-line agent in the treatment of seasonal and perennial allergic conjunctivitis has been controversial because of the potential side effects of long-term topical steroid use. Steroids have the potential to cause increased intraocular pressure (IOP), development of posterior subcapsular cataracts, and increased susceptibility to infections, especially viral and fungal infections. These complications may occur with any steroid use and are highly dependent on the duration of treatment, frequency of dosage, and concentration of the agent used. Steroid-induced IOP increase usually occurs after a few weeks and may occur months to years after initiation of therapy. Patients using steroids long term must be monitored for any of these potential side effects.

Until now, no studies have specifically investigated the long-term use of loteprednol etabonate 0.2%, with respect to its safety profile, in the treatment of seasonal and perennial allergic conjunctivitis.

**DISCUSSION**

Topical corticosteroids offer a wide range of anti-inflammatory treatment properties for ocular allergy and inflammation by reducing or inhibiting the release of the inflammatory chemical mediators throughout the inflammatory cascade. The long-term use of topical ophthalmic steroids for external inflammatory or allergic disease in clinical practices has been discouraged by concerns regarding their potentially harmful adverse effects, such as IOP increase, cataractogenesis, and the potential to aggravate certain infectious external diseases.

The safety profile of loteprednol etabonate has been linked to its chemical structure, which is similar to prednisolone; however, the ketone group found on the number 20 carbon molecule (found on all other ophthalmic steroids) is absent and has been replaced by an ester group. This specific ketone group at that position has been implicated in the formation of cataracts. This ester group is hydrolysed by tissue...
estimates so that it undergoes a rapid and predictable transformation into an
inactive metabolite. Loteprednol etabonate 0.2%

THE IMMUNOLOGY OF ALLERGIC CONJUNCTIVITIS

Ocular allergies appear to be the result of a combination of factors including genetics, early childhood exposure, environment, air pollution, and exposure to pets. Allergic conjunctivitis is an inclusive term that takes in a variety of allergy-related conditions including seasonal, perennial, vernal, and atopic allergies. Perennial and seasonal allergies are the most commonly encountered in clinical practice.

Allergic conjunctivitis is the result of an inflammatory cascade initiated by an allergen particle binding to an immunoglobulin E (IgE)-sensitised mast cell, leading to degranulation and release of a host of inflammatory mediators. The development of the allergic cascade appears to occur in three stages: sensitisation, the early phase, and the late or chronic phase.

SENSITISATION

In the sensitisation phase, an antigen is exposed to the ocular surface of an allergy-predisposed patient and is phagocytosed and “processed” into simpler peptides by antigen-presenting cells. The allergen particles are eventually presented on major histocompatibility complexes on the surface of the antigen-presenting cells, which induce T lymphocytes to start to generate type 2 T helper (Th2) cells and the production of inflammatory mediator. The immune system is primarily made up of type 1 T helper (Th1) cells, which are primed to protect the body from harmful bacteria and parasites. With the increased production of Th2 cells, an inflammatory cascade is primed to react to antigens from non-harmful antigens such as pollen. These Th2 cells activate the immune system B cells to produce IgE molecules that are sensitised to the particular allergen particle that initiated the process, and these sensitised IgE molecules bind to mast cells and basophils in the conjunctiva. This binding of the IgE antibody to mast cells and basophils is the hallmark of sensitisation.

EARLY PHASE

The early phase of allergic conjunctivitis occurs immediately and lasts for about 1 hour, when the sensitised IgE molecules come in contact with the antigen again. This is referred to as an immediate hypersensitivity reaction. The antigen binds to the IgE molecule, which is attached to mast cells and basophils in the conjunctiva, resulting in degranulation and the release of inflammatory mediators.

Histamines, leukotrienes, prostaglandins, and platelet-activating factor cause the symptoms of immediate hypersensitivity, such as blood vessel dilatation (hyperemia), increased vascular permeability/ fluid exudation (edema), and mucosal swelling. These symptoms characterise the initial response in allergy. Typically, an acute response is followed by a resolution phase, which involves the initiation of anti-inflammatory immune responses to restore normal physiologic function of the tissue. However, in certain individuals or under certain conditions, an acute inflammatory response leads to persistent and subclinical inflammation over a prolonged period of time, resulting in chronic disease.

LATE PHASE

The late or chronic phase occurs approximately 4 to 6 hours after the early phase and is characterised by the presence of allergic symptoms long after contact with the allergen. The late phase is secondary to the release of proinflammatory (interleukin [IL]-1, macrophage inflammatory protein, and tumor necrosis factor-alpha) and type 2 (IL-4, IL-5, and IL-13) cytokines. The production of these mediators results in the recruitment and activation of inflammatory cells, such as monocytes, T cells, eosinophils, and basophils. Analysis of conjunctival scrapings and tear samples shows an early accumulation of neutrophils, followed by the recruitment of eosinophils within 6-10 hours, and a later infiltration of lymphocytes.

Late-phase response leads to chronic inflammation of the ocular surface, which plays a major role in the pathophysiology of the most severe forms of ocular allergic disorders. Chronic inflammation can be secondary to persistent allergies (eg, perennial allergic conjunctivitis secondary to dust mites, pets, etc.), bacterial or viral infections, or autoimmune disease.

FINDING THE ANSWER

Patients will often know what they are allergic to, such as ragweed, pollen, or pet dander. However, patients may not know the specifics of their allergies, and skin prick tests are widely used to demonstrate an immediate IgE-mediated allergic reaction to determine a patient’s allergy list. SPTs represent a major diagnostic tool in the field of allergy, and, if properly performed, they yield useful evidence for the diagnosis of a specific allergy. Due to the many inherent complexities in SPT performance and interpretation, they should be carried out by trained health professionals.

CONCLUSIONS

Loteprednol etabonate has all the advantages of a steroid anti-inflammatory medication while sparing the steroid induced side effects of secondary glaucoma and cataract formation due to its improved side effect profile. Routine slit lamp examination and monitoring of IOP in patients using topical steroids should still be performed. In addition, Loteprednol etabonate 0.2% in its steroid anti-inflammatory capacity has the ability to block, reduce, or inhibit all of the inflammatory mediators along the cascade offering allergy sufferers relief of nearly all signs and symptoms associated with the ocular allergic response without the unwanted side effects.

References


**REVIEW OF ONCE-MONTHLY ORAL IBANDRONATE**

1. Ibandronate 150mg oral once monthly is indicated for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures.
   - A. True
   - B. False

2. The MOBILE trial was a non-inferiority BMD study that compared the efficacy and safety of three once-monthly oral ibandronate regimens with the ibandronate ___ daily regimen.
   - A. 1mg
   - B. 2mg
   - C. 2.5mg
   - D. 3mg.

3. Choose the correct statement:
   - A. Oral ibandronate 100mg once monthly provides twice the annual cumulative exposure to ibandronate compared to the 2.5mg daily formulation.
   - B. Oral ibandronate 150mg once monthly provides twice the annual cumulative exposure to ibandronate compared to the 2mg daily formulation.
   - C. Oral ibandronate 150mg once monthly provides twice the annual cumulative exposure to ibandronate compared to the 2.5mg daily formulation.
   - D. Oral ibandronate 200mg once monthly provides twice the annual cumulative exposure to ibandronate compared to the 2.5mg daily formulation.

4. Choose the correct statement:
   - A. The MOTION study which compared the efficacy of once-monthly oral ibandronate with weekly alendronate in women with postmenopausal osteoporosis showed that the two regimens were comparable at increasing BMD after 12 months at the lumbar spine only.
   - B. The MOTION study which compared the efficacy of once-monthly oral ibandronate with weekly alendronate in women with postmenopausal osteoporosis showed that the two regimens were comparable at increasing BMD after 12 months at the lumbar spine and total hip.
   - C. The MOTION study which compared the efficacy of once-monthly oral ibandronate with weekly alendronate in women with postmenopausal osteoporosis showed that the two regimens were comparable at increasing BMD after 24 months at the lumbar spine and total hip.
   - D. The MOTION study which compared the efficacy of once-monthly oral ibandronate with weekly alendronate in women with postmenopausal osteoporosis showed that the two regimens were comparable at increasing BMD after 12 months at the total hip only.

5. The VIBE study showed that monthly ibandronate-treated patients had a significantly lower risk of ___ fracture than weekly bisphosphonate patients.
   - A. vertebral
   - B. Hip
   - C. non-vertebral
   - D. All of the above.

6. Choose the correct option. The MOBILE-LTE study concluded that:
   - A. 150mg once-monthly oral ibandronate is an effective and well-tolerated treatment for postmenopausal osteoporosis.
   - B. The BMD at the proximal femur is maintained and there are further small gains in lumbar spine BMD.
   - C. The efficacy of ibandronate once monthly is sustained over five years and there were no new safety signals.
   - D. All of the above.

7. Choose the incorrect option. In the MOBILE and DIVA studies:
   - A. All-year data showed statistically significant reductions in the risk of key non-vertebral fractures for the high-dose ACE group compared with placebo.
   - B. All-year data showed statistically significant reductions in the risk of all clinical fractures for the high-dose ACE group compared with placebo.
   - C. Reductions in fracture risk for the low- and mid-ACE groups compared with placebo did not reach statistical significance for most of the fracture types examined.
   - D. The high-dose group (ACE ≥10.8mg) did not show significantly longer time to fracture vs placebo for key NFRs; all NFRs and all clinical fractures at two years.

INSTRUCTIONS: 1. Go to [www.medicalchronicle.co.za](http://www.medicalchronicle.co.za) 2. Click the tab labelled ‘CPD Portal’ on the far right tab near the top of the page. 3. Select the relevant questionnaire from the list and complete the form at [https://www.medicalchronicle.co.za/review-of-once-monthly-oral-ibandronate/](https://www.medicalchronicle.co.za/review-of-once-monthly-oral-ibandronate/)

**OCULAR ALLERGIES: SEASONAL ALLERGIC CONJUNCTIVITIS**

1. Classic symptoms of seasonal allergic conjunctivitis include:
   - A. Itching, eyelid swelling, burning
   - B. Stinging, conjunctival hyperemia
   - C. Chemosis, watery or mucoid discharge
   - D. All of the above

2. The Early Phase of allergic conjunctivitis occurs immediately after allergen exposure and lasts for about...
   - A. 4 - 6 hours
   - B. 2 hours
   - C. 1 hour
   - D. 30 minutes

3. The Late Phase is characterised by...
   - A. The release of histamine
   - B. The presence of allergic symptoms long after contact with the allergen
   - C. Degranulation of mast cells
   - D. None of the above

4. Topical vasoconstrictors with or without anti-histamines may provide acute relief, but when used for more than 5-7 days a possible rebound performance of symptoms may occur when medication is abruptly discontinued.
   - A. False
   - B. True

5. Topical mast cell stabiliser and anti-histamine combinations have the ability to reduce the release of many other inflammatory mediators because...
   - A. They are the most effective
   - B. They block histamine H1 receptors
   - C. They stabilise the mast cell membrane
   - D. None of the above

6. Topical ophthalmic steroids have the potential to block, reduce, or inhibit the production of virtually all inflammatory mediators along the inflammatory cascade.
   - A. True
   - B. False

7. Steroids do not block histamine receptors, they inhibit the synthesis of histamine in mast cells.
   - A. False
   - B. True

8. Steroids inhibit the degranulation of:
   - A. Mast cells
   - B. Basophils
   - C. Neutrophils
   - D. All of the above

9. The corticosteroid molecule with an improved safety side effect profile is
   - A. Prednisolone acetate
   - B. Loteprednol etabonate
   - C. Dexamethasone
   - D. All of the above

10. Steroids offer relief of nearly all signs and symptoms associated with the ocular allergic response.
    - A. Anti-histamines
    - B. Topical mast cell stabiliser/anti-histamine combinations
    - C. Vasoconstrictors
    - D. Topical ophthalmic steroids

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