Current Concepts in the Management of VKC

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Vernal keratoconjunctivitis is an acute-on-chronic inflammatory disease of conjunctiva and cornea; if not treated properly, it can result in sight-threatening complications. Mild cases tend to remit with nonspecific and supportive therapy but severe cases are more protracted, with frequent remissions and relapses and need immuno-modulating therapy.

Pathogenesis: It is mainly a Type I (immediate) hypersensitivity reaction which occurs when a sensitized individual comes in contact with a specific antigen. However chronicity of the disease is due to the involvement of T lymphocytes. These in turn result in proliferation of fibroblasts which lay down exuberant amounts of collagen fibers in the conjunctival tissue. Hence the following changes are observed:

Conjunctiva: Hyperplasia of conjunctival epithelium, marked cellular infiltration in adenoid layer, proliferation, increased permeability and vasodilation.

The Tarsal changes are typically seen in the upper tarsus comprising of proliferation of fibrous layer of conjunctiva and its hyalinization resulting in the formation of giant papilla (>0.3 mm), giving the classic 'cobble-stone' appearance. In severe cases, these papillae may undergo hypertrophy to produce cauliflower-like excrescences of 'giant papillae' which may cause mechanical ptosis.

The limbal form comprises of papillae which have a thick gelatinous appearance along with multiple white spots which are collections of degenerated epithelial cells and eosinophils called Horner-Trantas dots. They undergo rapid dissolution and do not last longer than a week.

The cornea affected in a variety of ways. **Punctate epithelial keratopathy** (PEK) results from the toxic effect of inflammatory mediators released from the conjunctiva. PEK can coalesce, resulting in frank **epithelial erosions** which coalesce to form a **shield ulcer**, which is typically shallow with white irregular epithelial borders. The major contributing factor in its development is chronic mechanical irritation from the giant tarsal papillae. Vernal **pseudogerontoxon** may be seen which is a degenerative lesion in the peripheral cornea resembling corneal arcus . **Keratoconus** is a frequent complication in chronic cases, associated with chronic eye rubbing and superimposed corneal thinning by injudicious use of topical steroids. **Corneal vascularization** may be seen rarely.

Symptoms of intense burning and itching, accentuated in warm humid atmosphere, are due to histamine and other inflammatory mediators. Associated

symptoms include mild photophobia, lacrimation, stringy discharge and heaviness of eyelids due to the tarsal involvement.

Differential Diagnosis: VKC has to be differentiated from Seasonal Allergic Conjunctivitis which is an acute Type 1 hypersensitivity reaction **involving only the conjunctiva**. There is marked chemosis and injection of the conjunctiva along with eyelid edema which is usually not seen in VKC. **Treatment**

1) Topical antihistamines: competitively and reversibly block histamine receptors and relieve itching, eye lid rubbing, conjunctival edema and redness. Their affect is temporary and symptomatic as they do not affect other pro-inflammatory mediators like prostaglandins and leukotrienes.

2) Mast cell stabilizers: They are used on a prophylactic basis to prevent mast cell degranulation on subsequent exposure to the allergen, on a long term basis. They include cromolyn sodium and lodoxamide (Alomide). However, drugs with both mast cell stabilizing ability and anti-histaminic property are the mainstay of therapy for mild forms of VKC like Alcaftadine, olopatadine, nedocromil and ketotifen.

3) Mucolytics: Acetyl cysteine (0.5%) for mucous plaque formation.This is not available as an ophthalmic preparation but it can be prepared by dissolving 10 mg powder from acetyl cysteine sachets (Mucolyte) in 10 cc distilled water.

4) Artificial tears: They help to dilute various allergens and inflammatory mediators that are present on the ocular surface and help flushing them. They also provide a barrier function and improve the first-line defense at the level of conjunctival mucosa. Hence eye drops during the day and eye ointment during the night is very helpful.

5) NSAIDs: they act on the cyclooxygenase metabolic pathway to inhibit the production of prostaglandins and thromboxanes which results in vasoconstriction, decrease in vascular permeability, leukocytosis, and a decrease on intraocular pressure e.g. ketorolac tromethamine

6) Vasoconstrictors: they provide short-term relief of vascular injection and redness and cause rebound conjunctival injection and inflammation. Hence they are of limited use or should not be used at all.

7) Corticosteroids: They are the most potent and popular amongst Ophthalmologists as a first line therapy. However, their prolonged, injudicious use results in a number of ocular adverse effects, such as delayed wound healing and resultant corneal thinning, secondary infections (viral, fungal), elevated intraocular pressure and formation of cataract. In addition, the anti-inflammatory and immunosuppressive affects are nonspecific.

8) Steroid-Sparing Drugs: In view of the numerous adverse affects of steroids, IMMUNE MODULATORY DRUGS, CYCLOSPORIN A and TACROLIMUS have been added to the armamentarium of therapeutic options available for severe VKC. They have minimal side-effects after prolonged usage. Marked subjective and objective improvement is noted within one month of therapy even in severe cases with marked corneal involvement.

Tacrolimus (fujimycin)[4-9]

It is a macrolide, discovered in 1984 from the bacteria *Streptomyces tsukubaensis*. It is similar in action to cyclosporine A but with a much higher potency (up to 100 times). It suppresses the activation, proliferation of B & T lymphocytes and formation of cytokines, especially interleukin-2. It is available as a topical preparation for the treatment of atopic dermatitis (eczema), vitiligo as 1.0% and 0.03% skin cream. It suppresses inflammation in a similar way to steroids, and is equally as effective but without any steroid related side-effects. The only known side effects are burning or itching sensation on initial applications, with increased sensitivity to sunlight and heat. Patients should minimize or avoid natural or artificial sunlight exposure. Skin infections should be cleared prior to application as there may be an increased risk of their activation.

Cyclosporin A eye drops: It has been used affectively for the treatment of VKC, Dry Eye Syndrome, Mooran's Ulcer, Corneal Melting, Scleritis. It is available as an ophthalmic preparation, Reastasis which are preservative free minims but only available as 0.05 %. It can be prepared in different strengths depending upon the severity of condition from Cyclosporin capsules which contain a water miscible gel. **For VKC, a concentration of 1%** is quite effective prepared by taking gel from 2 capsules of 50 mg each and maxing it with 4.5 cc distilled water. They cause a stinging sensation on instillation, apart from which, there are no known side effects upon prolonged usage. **Preservatives in commercial preparations kill the active ingredient;** since no preservatives are added, the drops prepared do not have a shelf-life and they have to be prepared fresh and dispensed weekly.

9) Treatment of large papillae: a single supra-tarsal injection of long-acting steroid along with immunomodulatory drugs affectively flattens the GPC. Protect the corneal surface with plenty of lubricant eye drops or a soft bandage contact lens if a shield ulcer is present; the ulcer gradually heals after continuing this therapy. There is no need to add steroid eye drops.

10) General Measures: Maintenance of an air-conditioned environment and control of dust particles at home and work may also be beneficial. Local measures, such as cold compresses, wearing dark goggles to prevent photophobia. Desensitization has also been tried without much rewarding results.

Conclusion:

VKC is a chronic, sight-threatening condition in children; if not treated appropriately, the vision is seriously and permanently affected either by the disease process itself like corneal opacities, keratoconus, corneal vascularization or due to injudicious use of steroids resulting in intractable glaucoma and corneal thinning promoting the keratoconus.

Unfortunately, topical steroids still remain a popular choice as a first line therapy amongst our ophthalmic fraternity. This article highlights new, safer and as potent drugs (Cyclosporin and Tacrolimus) as steroids but without any proven side effects after long term usage. This is because of the poor absorption of these drugs through cornea; they concentrate on the ocular surface and their affect is enhanced by prolonged use.

Hence **in mild cases**, prescription should include an anti-histamine, a mast cell stabilizer and lubricant eye drops during the day and a lubricant ointment at night for at least a month or two. There is no need for the addition of steroids at the acute stage which is mainly histamine-mediated.

In moderate to severe or recurrent cases, addition of immunomodulatory drug for at least 4-6 months becomes mandatory. The affect of both cyclosporin eye drops and Tacrolimus is additive. In children, try both but if they cannot tolerate the stinging of Cyclosporin eye drops, then continue only with Tacrolimus ointment applied in the conjunctival fornix twice a day for at least 2 months after all signs of VKC disappear.

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