

EDITORIAL

Immunosuppressant drugs in the treatment of allergic eye disease: do they have potential usage?

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The conjunctivae of the eye are exposed to the same wide spectrum of airborne allergens as is the nasal and bronchial mucosa, and also exhibit the same inflammatory allergic responses as these other body surfaces. Immediate and late responses to allergens and delayed hypersensitivity reactions have all been described with the involvement of mast cells, eosinophils, neutrophils, macrophages and T lymphocytes and the numerous mediators released by these cells. The inflammatory conditions that result from these reactions are classified as acute allergic conjunctivitis, seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis and giant papillary conjunctivitis [1, 2].

Acute, seasonal and perennial allergic conjunctivitis are relatively mild conditions, can occur at any age, and are usually caused by exposure to allergens of plant or animal origin such as grass or tree pollens and house dust mite. The predominant inflammatory cells are mast cells and eosinophils.

Vernal keratoconjunctivitis and atopic keratoconjunctivitis are, as the names imply, more severe inflammatory conditions involving the deeper layers of the eye. Vernal keratoconjunctivitis usually presents in boys less than 10 years of age. The symptoms are severe and distressing, intense itching, photophobia, blepharospasm and the production of thick tenacious mucus making it difficult to open the eyes in the mornings. The condition is characterized by subepithelial accumulations of lymphoid tissue forming papillary hypertrophic swellings – ‘cobblestones’. There is also infiltration with eosinophils, mast cells, macrophages and lymphocytes suggesting that both mast cell-IgE- and lymphocyte-mediated reactions are involved. Corneal erosion with plaques of mucus and fibrin preventing re-formation of the epithelium can occur and the resultant scarring is sight threatening.

Atopic keratoconjunctivitis has a similar profile of inflammation to the vernal type but primarily affects young adults. Corneal ulceration and scarring can occur as can the development of keratoconus, which may require the patient to wear contact lenses to correct sight.

Giant papillary conjunctivitis occurs in eyes in which the conjunctival surface is in contact with foreign material such as contact lenses. Clinically it has similar features to vernal keratoconjunctivitis.

The treatment of acute allergic, seasonal allergic and perennial allergic conjunctivitis consists of avoidance of the responsible allergen where possible and the application of antihistamine and anti-inflammatory eyedrops. Antihistamine eyedrops are effective in relieving the itching, oedema and hyperaemia associated with immediate hypersensitivity

responses. For more prolonged use, eyedrops containing one of the chromones, sodium cromoglycate or nedocromil sodium, have proven efficacy and safety.

In cases of vernal and atopic keratoconjunctivitis, although the chromones can be of benefit in both, it is usually necessary to resort to prolonged treatment with topical corticosteroids. However, long-term topical corticosteroids, as in other clinical situations can result in serious adverse events. Ocular hypertension or glaucoma can affect up to 20% of patients and longer administration can result in cataracts plus the possibility of enhancing infection, in particular herpes simplex keratitis. Although topical corticosteroids are nearly always needed to treat vernal and atopic keratoconjunctivitis, the amount used and the length of treatment can often be reduced by the concomitant use of topical chromones.

It would therefore be a major advance if an alternative anti-inflammatory agent to corticosteroids became available, particularly if it had equivalent efficacy and without the long-term side-effects.

In this issue of the journal, Sengoku et al. [3] from the Medicinal Biology Research Laboratories of Fujisawa Pharmaceutical Co. Ltd. in Japan report on a series of animal experiments in models of allergic eye disease using the immunosuppressant drug tacrolimus hydrate, also known as FK506. Tacrolimus hydrate is a macrolide extracted from the soil bacterium *Streptomyces tsukubaensis* [4]. It was developed originally as an immunosuppressant and is used worldwide to prevent liver and kidney allograft rejection. More recently, it has been approved in a number of countries as a topical skin ointment for the treatment of moderate to severe atopic dermatitis in adults.

Sengoku et al. [3] report the effects of tacrolimus in animal models of late and delayed hypersensitivity reactions in the eye. A late response in rats and guinea pigs was induced by the topical application of egg albumin solution 2 weeks after the animals had been sensitized by intra-peritoneal injection of egg. Delayed responses were induced in rats, guinea pigs and rabbits by the injection of purified protein derivative into the palpebral conjunctivae 2 weeks after sensitization with subcutaneous injections of complete Freund's adjuvant. In the case of late responses, the conjunctivae were examined microscopically 24 h after challenge in the case of the rat and 6 h after challenge in guinea pigs. Delayed responses in the rat and guinea pig were evaluated by measuring the amount of Evans Blue dye leaking into the palpebral conjunctiva, 20 h after challenge. Delayed responses in the rabbit were evaluated by direct examination of the eyes in the live animal, 24 h after challenge.

Eyedrops containing tacrolimus hydrate, placebo or the corticosteroids betamethasone sodium phosphate or fluorometholone were instilled in the eyes either before or both before and after challenge. Tacrolimus hydrate eyedrops significantly reduced the severity of the induced conjunctival inflammation, the numbers of T cells and eosinophils infiltrating in the late response, and the amount of dye extravasated in the delayed response in the rat model, the effect being comparable to that of the corticosteroids. There was a significant reduction in the conjunctival inflammation score in the late response in the guinea pig model. There was also a significant reduction in the amount of dye extravasated in the delayed response in the guinea pig, a model in which corticosteroids are without effect. Both tacrolimus and corticosteroids produced a significant reduction in the severity of inflammation in the rabbit model.

These experiments and the results obtained are described in some detail to make the point that these are complex experiments in animal models and some caution is necessary before extrapolating to speculate on the potential of this drug in allergic eye disease. While the results presented in this paper are of great interest, more work is required before its use in human disease can be properly evaluated.

Tacrolimus is a very potent drug similar in its mode of action, but chemically different, to cyclosporine. Both drugs were originally developed to prevent the rejection of transplants, which remain their main use. The primary mode of action is the inhibition of the formation of cytotoxic lymphocytes which are mainly responsible for graft rejection. Tacrolimus suppresses T lymphocyte activation, T helper cell-dependent B cell proliferation, the formation of lymphokines, specifically IL-2, IL-3 and γ -interferon and IL-2 receptor expression [5].

A skin ointment of tacrolimus has recently been licensed for the treatment of moderate to severe atopic dermatitis in adult patients [6]. The data sheet states that 50% of patients experience some type of skin irritation adverse reaction and patients may be at an increased risk of folliculitis, acne and herpes simplex. While these may be manageable when the drug is applied to the skin, if it is planned to make use of the drug in treating allergic eye disease adequate evidence of the safety profile in the eye and whether these are possible or real risks will be necessary.

The first trials of the use of this type of compound were published in 1990 and 1991, short-term trials on the use of cyclosporine in vernal keratoconjunctivitis [7, 8]. In both cases there was a significant and clinically useful improvement in symptoms and signs. Adverse effects were reported as mild, being transient discomfort and minor epithelial changes in one case and none in the other. However, the length of treatment was short, being 2 months in one and 6 weeks in the other. In the trial in which it was measured, there was no significant change in intraocular pressure during or after treatment. Despite these positive findings, no licensed product of cyclosporine eyedrops has appeared in the intervening

years until approval was given by the United States Food & Drug Administration for a 0.05% cyclosporine ophthalmic emulsion in December 2002. However, the indication for this product is keratoconjunctivitis sicca (dry eye disease) and not allergic eye disease. Information provided by the company stated that the most common adverse effect was ocular burning (17%), with hyperaemia, discharge, pain, foreign body sensation, itching, stinging and blurring of vision being reported at an incidence of 1–5%. There are no reports of increased risk of infection. Although the data sheet lists all the potential systemic adverse effects of the compound, it also states that it was not possible to detect blood levels of cyclosporine after topical administration in the eye during 12 months of usage. This suggests that the risk of major effects on the immune system from the topical use of the drug in the eye is low.

On the basis, therefore, of existing evidence (the report published in this issue of the journal, the previous reports of the use of cyclosporine in vernal keratoconjunctivitis and the safety profile of the recently released cyclosporine product in the USA), there is considerable potential for the use of these agents as an alternative to corticosteroids in severe allergic eye disease. Further trials of their usage in this indication will be awaited with interest.

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