

# Ocular anti-allergic action of mapracorat, a novel selective glucocorticoid receptor agonist, involves eosinophil's apoptosis

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Ocular allergy is a disease primarily characterized by an inflammatory response of the conjunctival mucosa and the term 'allergic conjunctivitis' refers to a collection of disorders that affect lid, conjunctiva, and/or cornea. Although allergic conjunctivitis is not generally life threatening, the symptoms of ocular allergy may have a significant impact on quality of life.

Allergic eye diseases are usually associated with type 1 hypersensitivity reactions, which cause early- and late-phase responses. Clinical symptoms and signs such as itching, chemosis, and congestion, driven primarily by mast cell degranulation, are manifested very quickly. This phase is followed by a late response after 6-24h, involving eosinophil and neutrophil infiltration into the conjunctiva (Baiula et al, 2012).

Glucocorticoids are the most effective anti-inflammatory drugs used to treat eosinophil disorders as they can prevent eosinophil accumulation and activation, and induce eosinophil apoptosis *in vitro* (McColl et al, 2007). Unfortunately, their anti-inflammatory and immunosuppressive effects are frequently accompanied by undesired side effects that may limit their use. Novel dissociated glucocorticoids can prevent eosinophil accumulation and induce apoptosis of eosinophils, making them promising candidates for ophthalmic drugs (Baiula et al, 2011).

Among them, mapracorat displays topical anti-inflammatory activity but is less effective in transactivation and, therefore, has less potential for side effects (Baiula et al, 2012). To date, the potential anti-allergic activity of mapracorat in the eye and whether eosinophils are targets of its action has been explored very little.

This study investigated the potential anti-allergic activity of topical mapracorat in a guinea pig model of allergic conjunctivitis. Effects on clinical score, eosinophil accumulation, CCL5, CCL11 and IL-1b mRNA levels and cell apoptosis in the conjunctival tissue were determined. We focused on eosinophils since these cells mediate unique cytotoxic and inflammatory effects by generation, storage, and release of their granule and the production of cytokines, growth factors, reactive oxygen species, and proinflammatory lipid mediators. Their recruitment and activation are regarded as crucial to the development of allergic disorders, including conjunctivitis. Besides selective migration, longer cell survival and decreased apoptosis are relevant to tissue-specific accumulation of these inflammatory cells (Ono and Abelson, 2005). Guinea pigs were actively immunized by i.p. injection of ovalbumin (OVA) and 3 weeks later challenged with OVA instilled into the conjunctival sac. Eye drops containing different concentrations of mapracorat or dexamethasone were administered 45 minutes before or two hours after OVA challenge.

Mapracorat or dexamethasone eye drops induced an analogous reduction in clinical symptoms of allergic conjunctivitis. OVA instillation in the eye of sensitized guinea pigs causes a marked elevation of eosinophils in the conjunctival area whereas their number is markedly reduced following dexamethasone or mapracorat treatment. Moreover, mapracorat and dexamethasone caused an increased eosinophil apoptosis in inflamed conjunctiva *in vivo*. Interestingly, mapracorat was more effective than dexamethasone to induce cell apoptosis.

In conclusion, mapracorat topically administered either before or after ovalbumin challenge was efficacious similar to dexamethasone, in preventing or in reducing ocular inflammatory responses to OVA exposure in sensitized guinea pigs. This action involves a reduction in gene expression of chemokines and cytokines, as well as a reduction in eosinophils, at least in part, likely due to increased conjunctival eosinophil apoptosis.

To our knowledge, this is the first study demonstrating that glucocorticoids, and in particular the SEGRA mapracorat, induce eosinophil's apoptosis *in vivo* at ocular level and this effect could be useful for their anti-allergic action.