

Cyclosporin ophthalmic emulsion

Elke Theander, Rolf Manthorpe

Sjögren's Syndrome Research Centre, Department of Rheumatology, Malmö University Hospital, Malmö, Sweden

The drug

Since 1983, cyclosporin A (CyA) has been commercially available for prevention of graft rejection in solid organ transplants and treatment of autoimmune diseases such as rheumatoid arthritis, severe plaque psoriasis and other indications. It is an immunomodulatory drug, selectively blocking Th1-lymphocytes in G₀ and G₁ phase of the cell cycle (1). It inhibits the transcription of DNA and prevents accumulation of mRNA for several cytokines. Interleukin-2 and interferon-gamma dependent immune reactions are blocked, leading indirectly to reduced tumor necrosis factor (TNF) alpha expression (2). Cyclosporin directly inhibits intracellular phosphatases such as calcineurin. CyA has no effect on hematopoietic cells and does not compromise macrophage function, thus leaving the host's immune defence unaffected. The therapeutic concentration in whole blood is between 40 and 400 ng/ml. The limit of detection with standard methods is around 15 – 30 ng/ml.

CyA as ophthalmic emulsion

Earlier topical CyA preparations, used for prevention of corneal transplant rejection or other severe ocular surface conditions including KCS in Sjögren's Syndrome, were oil-based ointments, since CyA is water insoluble. These ointments frequently caused blurred vision and irritation (3,4). The ophthalmic emulsion now produced by Allergan is an oil/water-based system containing different concentrations of CyA. The subjective side effects are commonly mild with transient burning or reddening and usually not leading to discontinuation of the treatment.

The problem of dry eyes, Keratoconjunctivitis sicca (KCS)

KCS may or may not be associated with Sjögren's Syndrome (SS). When appearing without SS, the population affected consists predominantly of postmenopausal or pregnant females or women taking birth control pills. These women either have reduced or elevated oestrogen levels, and all have a relatively reduced androgen level and often disturbed androgen/prolactin balance. Oestrogen receptors are not found in the lacrimal gland (5). Androgens have a trophic and anti-inflammatory effect in the lacrimal gland (6). High levels of prolactin seem to impair glandular function (7). CyA binds to the same receptor as prolactin, and blocking prolactin activity may result in restoration of the balance between prolactin and androgen activities locally in the eye (8).

In KCS lymphocytic infiltration in the lacrimal gland as a primary or secondary event in the disease process leads to local cytokine production. Interleukin-1 and TNF-alpha have been shown to inhibit the basal and stimulated tear response (9). The proinflammatory cytokines flow together with the tears onto the ocular surface where they induce inflammation and cytokine production (10). The cytokines on the ocular surface may disrupt the normal neural afferent signals leading to interrupted secretomotor nerve impulses to the lacrimal gland (11). Autoantibodies against lacrimal gland M3 muscarinic acetylcholine receptors may block neural efferent secretory impulses (12). Normal tear secretion from lacrimal gland acinar cells occurs under neural control due to ocular surface reflexes and sympathetic and parasympathetic efferent pathways. The ocular surface, lacrimal gland and reflexive innervation are seen as a functional unit. Without neural stimulation the lacrimal gland shows atrophy and abnormal apoptosis. This results in further impairment of tear production and increased inflammatory infiltration and the dry eye disease cycle is established.

Goals of therapeutic intervention in KCS

- Decrease of lacrimal gland inflammation and improved gland function.

- Normalisation of the tear film.
- Decrease of ocular surface inflammation.
- Improvement of neural feedback mechanisms.

Current treatments for dry eyes/ KCS

The local topical treatment options with tear substitutes are discussed in another lecture. They ameliorate the ocular discomfort and are important for the patient but do not profoundly influence the dry eye disease cycle with lacrimal gland inflammation and neural feedback dysfunction. Systemically used herbal drugs such as Bromhexine and Gammalinolenic acid may have some stimulating effect on tear production and reduce ocular surface inflammation. In controlled studies, these effects are moderate and the clinical significance is questionable (13, 14). Pilocarpine-HCL has a clear stimulatory effect on salivary glands and some effect on tear secretion in clinical studies (15). As pilocarpine does not influence the cytokine production by the inflammatory cells in the lacrimal gland infiltrate, the effect on the ocular surface may be even proinflammatory despite more tears. None of these drugs has an immunosuppressive effect. However, gammalinolenic acid theoretically might have an immunomodulatory effect due to changes in prostaglandin-synthesis (16).

Contradictory results have been reported regarding the effect of Hydroxychloroquine on lacrimal gland function (17,18). Systemic immunosuppressive treatment for Sjögren´s Syndrome associated KCS has never been documented effective. An open-label pilot trial with interferon alpha-2 showed promising results (19). Systemic CyA has been tried without convincing effects (20).

Rationale for CyA ophthalmic emulsion in Sjögren´s Syndrome associated KCS

The use of topical CyA gives the advantage of high local concentrations of the drug on the ocular surface and thus strong immunomodulatory effect in combination with low systemic toxicity due to extremely low concentrations in whole blood. Preclinical studies have shown rapid absorption into the ocular surface tissue, with highest concentrations in cornea, conjunctiva and sclera. In the lacrimal gland tissue, CyA concentrations were 12 fold higher than in whole blood. The corneal tissue works as a kind of reservoir allowing redistribution of CyA to the other surface tissues. Elimination from ocular tissue is slow. (Results from preclinical pharmacokinetic and toxicological studies by Allergan. AGN reports).

Results of topical CyA treatment in KCS in preclinical studies

Reduced lymphocyte infiltration is seen in conjunctival and lacrimal gland tissue. This results in reduced secretion of proinflammatory cytokines and normalised apoptosis in the lacrimal gland. Normalisation of autonomic nerve traffic between ocular surface as well as main and accessory lacrimal glands is expected due to the less injured ocular surface. (Results from the Dry Eye Dog Model Studies by Allergan. AGN reports).

Results from early clinical studies (phase II)

Topical CyA in concentrations between 0.05% and 0.4% reduced the signs and symptoms of dry eye disease. The most significant improvements were seen in rose bengal staining and the subjective experience of sandy and gritty feeling, itching and dryness. The benefits persisted often into the posttreatment period. No ocular infections or microbial overgrowth were observed. There were no systemic adverse events and only mild local adverse effects such as burning and irritation up to minutes after application. The CyA blood levels for the lower concentrations of the ophthalmic emulsion were <0.1ng/ml and 0.16ng/ml in the highest concentration. (Results from a dose-ranging study, evaluating the safety, tolerability and efficacy of Cyclosporine Ophthalmic Emulsion conducted by Allergan. AGN report)

Ongoing clinical studies (phase III)

Both in the USA and in Europe, placebo-controlled multicentre studies examining the efficacy and long-term safety of CyA ophthalmic emulsion (0.05% and 0.1%) are now being conducted. A total of 1260 patients were randomised. The target population is patients with moderate or severe KCS with or without coexisting Sjögren's Syndrome. At present, March 1999, the double-blind study phase is ongoing and no results have been presented.

Conclusion

CyA as an ophthalmic emulsion in preclinical and early clinical studies appears to have the potential to interrupt the negative dry eye cycle by inhibition of T-cell mediated local ocular inflammation. Consequently, signs and symptoms of KCS are reduced. Large placebo-controlled studies currently being performed may show the degree of efficacy and long-term safety of this first immunomodulatory drug specifically designed for treatment of KCS.

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