TACROLIMUS IN OPHTHALMOLOGY

Abdul Waris[1], G K Nagpal[2], Gargi Nagpal[3,*], Naheed Akhtar[4]

[1]Assistant Professor, [3]Junior Resident II, AMUIO, Aligarh
[2]Nagpal, Senior Eye Surgeon, Nagpal Eye Care & Research Centre, Aligarh
[4]Eye Surgeon, Gandhi Eye Hospital, Aligarh.

***Corresponding Author:**
Email: garginagpal@rediffmail.com

ABSTRACT

Tacrolimus is a 23 member cyclic macrolide lactone and was isolated from Streptomyces tsukubaensis in 1984.[1] it has been shown in vitro and in vivo to be a potent immunosuppressive agent. It is 100 times more powerful than cyclosporine in vitro in inhibiting T-cell proliferative responses, including mixed lymphocyte reactivity and cytotoxic T-cell generation. This immunomodulator has increasing number of implications in various aspects of ophthalmological conditions, the battle against them so far having been fought with corticosteroids, which are themselves a double edged sword. In this article we will be going through various studies which have thrown light on the future potential of applications of tacrolimus in ophthalmology.[2]

Key Words: *allergic conjunctivitis, dry eye disease, tacrolimus, immunomodulation, uveitis, graft versus host disease*

INTRODUCTION

FK506 (tacrolimus hydrate) is a novel macrolide immunosuppressant discovered in 1984 by the Exploratory Research Laboratories of Fujisawa Pharmaceutical Co., Ltd. (Osaka, Japan) and is now used as an immunosuppressant after organ transplantation worldwide. It has a mechanism of action similar to that of ciclosporine A, but is 50–100 times more potent and less likely to induce systemic hypertension and lipid abnormalities. Its mechanism involves binding to the cytoplasmic FK506-binding protein (FKBP-12). The complex inhibits the Ca^{2+}- and calmodulin-dependent dephosphatase activity of calcineurin, which inhibits the ability of calcineurin to dephosphorylate the nuclear factor of activated T cells (NFAT), a transcription factor that activates the genes of interleukin (IL)-2, 4, 5 granulocyte macrophage colony-stimulating factor, tumor necrosis factor, interferon, and other ILs that are required for the development of an immune response. In 1989, Kobayashi first reported that FK506 suppressed corneal graft rejection in rabbits. Since then, the use of FK506 is of special interest in ophthalmology because it is indicated to be effective in the treatment of immune-mediated diseases such as corneal graft rejection, ocular inflammation, ocular pemphigoid, and uveitis.[3] Topical tacrolimus ointment is commercially available in two strengths 0.03% and 0.1%.[4] The present review is an attempt to present a coherent picture of the recent successful applications of tacrolimus in ophthalmology.

DISCUSSION

Allergic eye diseases comprise a spectrum of diseases, with each condition being characterized by a complex immunopathology. The more severe and chronic conditions, such as vernal keratoconjunctivitis and atopic keratoconjunctivitis, involve predominantly mast cells and eosinophils, while also being associated with a preponderance of T cells. Treatment with topical antihistamines or mast cell stabilizers is often unsatisfactory, and therapy depends on topical corticosteroids. Corticosteroids have significant side-effects with long-term use; therefore, they appear to be more appropriate for short-term pulse therapy. Immunomodulatory agents can also be used to inhibit T-cell activation and show encouraging results among patients with severe allergic eye conditions.[5]

For severe disease, VKC most frequently occurs in children and young adults, while AKC typically begins in the late teens or early twenties, with AKC persisting into the fourth or fifth decade of life.

Therefore, it is desirable to avoid long-term steroid use, particularly during childhood, to reduce the lifelong risk of developing steroid-related complications.[1] In accordance with the previous report, the present study by Atsuki Fukushima, et al., showed that tacrolimus eye drops were effective in treating severe allergic ocular diseases with giant papillae or corneal involvement. In addition, twice daily tacrolimus eye drop treatment significantly reduced the ocular sign and symptoms even in patients who earlier had a poor response to topical cyclosporine.[1] Also, the study showed that 53.4% of patients using steroids were successfully weaned from topical steroid therapy, thus, tacrolimus eye drops having a steroid-sparing or replacing effect. Because those in infancy or early childhood are at high risk for steroid-induced elevation of intraocular pressure, tacrolimus eye drops may be a very effective, alternative treatment for VKC or AKC that does not impose the risk of developing glaucoma.[1]

Corneal infection, bacterial keratitis and bacterial corneal ulcer were the few undesirable effects post tacrolimus use, necessitating a close monitoring during topical tacrolimus therapy in cases of prolonged use. However, a previous study examining cyclosporine 0.1% aqueous ophthalmic solution showed a similar incidence of corneal infection, suggesting that tacrolimus eye drops are equivalent to cyclosporine for the indications studied here.[1] Tacrolimus treatment may cause adverse reactions, including renal failure, when used systemically. In our study, no serious systemic adverse events were observed, which was likely because the percentage of tacrolimus reaching the bloodstream with twice-daily topical use is very low. In conclusion, the efficacy and safety of tacrolimus eye drops in patients with VKC or AKC in a clinical setting was evaluated. Our results suggest that topical tacrolimus therapy is safe and effective in treating patients with severe allergic conjunctivitis.[1] Also, Zribi H, et. Al, in their study showed dramatic improvement of atopic keratoconjunctivitis after topical treatment with tacrolimus ointment restriced to the eyelids.[6] Topical tacrolimus 0.03% was also found to be effective in the treatment of steroid resistant subepithelial infiltrates, seen after adenoviral keratoconjunctivitis.[5] In a study by Kymionis GD, et al, topical tacrolimus 0.03% ointment appeared to be an effective alternative treatment for severe Giant papillary conjunctivitis, refractory to conventional treatment.[7] Safety and efficacy of tacrolimus in the treatment of atopic dermatitis have been demonstrated in short- and long-term studies with adult and pediatric patients in a study by Tais Hitomi Wakamatsu and colleagues.[8]

In a study done by Freeman AK, et al, on "The safety and efficacy of tacrolimus ointment 0.1% in the treatment of atopic dermatitis of the eyelids", tacrolimus ointment 0.1% was applied twice daily on eyelids for 8 weeks and were followed for 2 additional weeks after the last day of treatment. Results revealed marked improvement in symptoms in 8 weeks with adverse events limited to local burning and itching after the first few applications of study medication and no statistically significant increase in intraocular pressure (IOP) during the study when compared with baseline. None of the patients developed cataracts or glaucoma during the study. In summary, tacrolimus ointment 0.1% was found to be a safe and effective treatment option for patients with moderate to severe eyelid dermatitis.[9]

Standard treatment of ocular cicatricial pemphigoid involves systemic immunosuppression since topical anti-inflammatories are ineffective. Hence, mortality associated with this disease is due to iatrogenic complications. Tacrolimus exhibits extremely good penetration of the conjunctiva. In a study done by Michel JL, Gain P, administration of tacrolimus at a concentration of 0.06% 3 times daily in 15 patients with inflammatory disease of the conjunctiva or the cornea, improvement was seen in 10 of these patients at 26 weeks. Oral tacrolimus cannot be used to control cicatricial pemphigoid refractory to standard immunomodulators. There were cases involving topical treatment of cicatricial pemphigoid, which showed marked efficacy with 2 to 6 months of treatment, with complete tolerability. Thus, topical tacrolimus appears to constitute an interesting alternative treatment in cicatricial pemphigoid.[10]

Dry eye disease (DED) is a multifactorial disease of the tears and ocular surface that causes tear film instability with potential damage to the ocular surface. The prevalence of dry eye in the world population ranges from 6 to 34 % with higher incidence in those aged over 50, affecting mainly women. Strategies for treating DED have recently been modified and include patient education, tear substitute, corticosteroids, secretagogues, fatty acids, immunomodulators, occlusion of lacrimal puncta surgery and, tarsorrhaphy.[11] In a study by Moscovici BK, et.al, topical 0.03% tacrolimus eye drops successfully improved tear stability and ocular surface status in patients with dry eyes. Also, study done by Sanz-Marco E, et.al, showed similar results.[12] Primary low-risk corneal transplants have the highest success rate (>90%) and lowest rejection rate (11–18%) of all transplant surgery and do not routinely require systemic immunosuppression. Factors that are recognised to increase the risk of rejection in corneal transplants include vascularisation in the recipient cornea, large graft size, HLA-A and HLA-B incompatibility, previous failed corneal graft/s, decreasing age of recipient, glaucoma, peripheral anterior synechiae, chemical burn and Herpes Simplex Viral Keratitis (HSVK), and such cases often require aggressive immunosuppression in order to avoid graft rejection.[13] Though, immunosuppression with topical steroids is considered the gold standard for all corneal grafts, the use of topical steroids is associated with increased intraocular pressure, cataracts or a recurrence of HSVK in susceptible patients. Also, In high-risk grafts, topical steroids alone are not sufficient to prevent rejection and systemic immunosuppression is often required, and so is the manifold increased chances of associated adverse events.[13]

Corneal graft rejection is a T cell-mediated immune response, hence, immunosuppressive drugs classed as T-cell inhibitors could be considered in the prevention and management of corneal graft rejection. In a study by A Joseph, et.al, tacrolimus was found to be effective and safe in the treatment of certain immune-mediated diseases (uveitides), including keratoplasty. The main side effect observed amongst the tacrolimus receipients in the study was hypertension, which was controlled well with antihypertensive drugs. Other side effects like raised serum creatinine, pancreatitis and lymphopenia were well normalised with a reduction in drug dose. Hence, indicating the applications of tacrolimus in post-operative cases of corneal transplantation.[13] In a similar study by Jung JW, et. al, it was found that long term maintenance treatment with tacrolimus ointment could be useful and safe for local treatment of ocular surface inflammation in chronic ocular GVHD.[14] Turgut B, et al, in their study found that systemic and topical tacrolimus may be beneficial in the prevention of corneal neovascularisation, through its effect on VEGF.[15] Topically administered tacrolimus (0.3mg/ml, 4 times a day), was also found to reduce postoperative subconjunctival scarring response 2 weeks after experimental glaucoma filtration surgery.[16] Experimental autoimmune uveoretinitis (EAU) is an inflammatory disease model that shares many clinical and histological features with human uveitis such as Behçet's disease, Vogt–Koyanagi–Harada disease and sarcoidosis. In EAU-susceptible strains of rat, immunisation with retinal antigen such as S-antigen or bovine interphotoreceptor retinoid-binding protein peptide induces T helper cell 1-mediated disease inflammatory response in the eye. This experimental model is useful for analysing the immunopharmacology of various immunosuppressive agents in uveitis.

In a study by Keiko Oh-i, et al., it was found that Intravitreal injection of tacrolimus was highly effective in suppressing the ongoing process of EAU without any side effects on systemic cellular immunity, and hence, this treatment may be useful in the management of patients with severe uveitis.[17]

CONCLUSION

Tacrolimus (FK506) has been used successfully as a systemic immunomodulator for more than 2 decades, and numerous studies have investigated its mechanisms of action. Systemic and topical tacrolimus have been investigated as treatments for ocular surface disorders that may have an immune-based

inflammatory component. In these studies, tacrolimus has shown efficacy in allergic conditions of eye, corneal graft rejection, inflammatory conjunctival and corneal diseases, uveitis, and graft-versus-host disease. As these disorders are often refractory to other available treatments, ophthalmic or systemic tacrolimus is a welcome nontoxic adjunct or replacement to potentially toxic topical or systemic immunosuppressive therapies used earlier.[18]

However, it has considerable side effects and appropriate caution should be exercised in its use. Proper patient selection and information is important before instituting treatment with tacrolimus.[13]

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