Tacrolimus for Ophthalmic Use: An Update

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Abstract

Tacrolimus, a macrolide isolated from a strain of Streptomyces, is an immunosuppressant and is used in cases of organ transplantation. It has a mechanism of action similar to that of cyclosporine. It is a lipophilic molecule which blocks the early phase of T-cell activation, thus inhibiting both T-lymphocyte signal transduction and IL-2 transcription. It is also inhibits the release of histamine from mast cells and impairs prostaglandin synthesis. Tacrolimus has shown to be effective in the treatment of immune-mediated diseases such as corneal graft rejection, ocular inflammation, ocular pemphigoid, and uveitis. In this article, we have tried to update the uses of tacrolimus in ophthalmology.

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Tacrolimus (FK506)[1] is a novel macrolide immunosuppressant isolated from a strain of Streptomyces and is now used for transplantation worldwide. It has a mechanism of action similar to that of cyclosporine. Clinical trials of tacrolimus in liver, kidney, and pulmonary transplantation have shown it to be more effective than cyclosporine,[2-4] and less likely to induce systemic hypertension and lipid abnormalities.[2,5-7]

Outside the field of transplantation, tacrolimus ointment[8-10] is currently available for treatment of atopic dermatitis in some countries. Tacrolimus ointment has higher efficacy and fewer adverse effects than corticosteroid ointments.[11] In 1989, Kobayashi et al.[12] first reported that tacrolimus suppressed corneal graft rejection in rabbits. Since then, the use of tacrolimus has been of special interest in ophthalmology because it was shown to be effective in the treatment of immune-mediated diseases such as corneal graft rejection,[13,14] ocular inflammation,[15,16] ocular pemphigoid,[17] and uveitis.[18-20]

Tacrolimus: Mechanism of Action

Tacrolimus is an 822 kDa immunosuppressant in the macrolide family, which is grouped with cyclosporine. Its action is initiated by binding to a class of peptidyl-prolyl cis-trans isomerases (PPIases), designated FK506-binding proteins (FKBPs). The predominant FKBP in the T lymphocyte is a cytosolic protein of approximately 12 kDa, and is designated as FKBP-12.[21,22] It is a lipophilic molecule which blocks the early phase of T-cell activation, thus inhibiting both T-lymphocyte signal transduction and IL-2 transcription.[23] Furthermore, it is also reported that tacrolimus inhibits the release of histamine from mast cells and impairs prostaglandin synthesis in its de novo way.[24] It also suppresses the histamine release and these three actions together may reduce allergic symptoms.[25]

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Systemic Use of Tacrolimus as an Immuno suppressant and Immunomodulator

Systemically administered tacrolimus was introduced to prevent rejection of solid organ transplants. It was first approved by the US FDA for use in liver transplantation.[26] Tacrolimus is available as an intravenous formulation (5mg/mL) and as sustained-release capsules (0.5, 1, 3, and 5 mg). Dosages are titrated to target blood levels. The large differences in the pharmacokinetics of tacrolimus between individuals make it hard to predict what drug concentration will be achieved with a particular dose or dosage range.[27]

Orally administered tacrolimus is also used for treatment of rheumatoid arthritis,[28] moderate to severe psoriasis,[29] and inflammatory bowel disease,[30] often in combination with other therapeutics. Lower daily doses (1.5–3 mg/day) than for transplant patients are used for these conditions. Systemically administered tacrolimus immunosuppressive therapy has been useful in controlling rejection following limbal allograft surgery,[13] as well as for severe ocular inflammatory conditions such as uveitis[18-20] and Behcet's disease. Daily doses of 1–2 mg/day are used for ocular inflammatory conditions

Pharmacokinetics of topically administered Ophthalmic Tacrolimus

Tacrolimus is a hydrophobic molecule which means that aqueous solutions at clinically useful concentrations are

likely to be unstable. Attempts to overcome this have led to ophthalmic tacrolimus prepared in castor oil,[31] olive oil,[32] and dextrin.[33] However, burning, redness, itching and epithelial keratitis limit the use of such oil vehicles. To address the problem of tacrolimus's limited ability to penetrate the cornea and reach effective therapeutic intraocular concentrations, several vehicles have been tested to improve its intraocular penetrability. Tacrolimus encapsulated in cyclodextrin has shown good intraocular distribution to prevent or delay corneal allograft rejection.[32] Liposome was also found effective as a carrier to deliver higher tacrolimus concentrations into all ocular tissues compared with olive oil.[32] Because of the extremely low blood concentration of tacrolimus after topical administration in animal models, systemic adverse effects are not anticipated, which will ease short-term safety concerns in clinical use.

Pharmacology of Ophthalmic Tacrolimus

Reduction of proinflammatory cytokines: Tacrolimus dramatically decreases CD4+ and CD8+ T-cell infiltration in corneal allografts, when administered topically. This is the result of the immunosuppressive role of tacrolimus in suppressing T-cell mediated lymphokines, IL-2 receptor expression, and the generation of cytotoxic T cells.[1] CD68 is a marker of antigen-presenting macrophage cells and plays an important role in allograft rejection. Corneas treated with tacrolimus showed fewer CD68+ cells. This indicates that tacrolimus may inhibit the migration of macrophages into corneal grafts, thus reducing the amount of allograft antigen presented to naive T cells through indirect pathways.

- ***Reduction of Activated T Lymphocytes:*** Tacrolimus forms a complex with FKBP intracellularly, and the complex eventually inhibits T-lymphocyte signal transduction.
- ***Effect on Conjunctival Epithelium and Goblet Cell Density:*** Squamous metaplasia, a condition of increased proliferation and abnormal differentiation of the conjunctival epithelium, may be observed by stained impression cytology and biopsies from aqueous tear-deficient dry-eye patients. It was shown in several animal models that tacrolimus eye drops inhibited inflammatory cell infiltration and also inhibited both the loss of conjunctival epithelium and decrease in the number of goblets cells, which play an important role in mucus secretion. Tacrolimus may confer protection of barrier function in the eyes, via normalization of the allergen-exclusion system.
- ***Neuroprotective Effect:*** Tacrolimus has been shown to exert profound neuroprotective and neuroregenerative effects in vivo and in vitro.[34] It has been shown that intravitreal injection of tacrolimus up-regulated the gene expression of neuroprotection-related molecules as well as decreased the expression of inflammatory responses related genes. These data support the notion that increased expression of neuroprotection-related genes by intravitreal injection of tacrolimus may play a potential role in retinal protection of the eyes with ongoing ocular inflammation, as well as in immune regulation.
- ***Reduced Markers of Apoptosis:*** Molecular markers of apoptosis, such as CD40, CD40 ligand (CD40L, also known as CD154), and Fas, have been shown to be elevated in the conjunctival epithelia of ocular inflamed patients. The anti-inflammatory and antirejection effects of tacrolimus may be partly due to blockade of CD40–CD154 interaction.

Clinical Effects of Ophthalmic Tacrolimus

Corneal Graft Rejection

Corneal transplantation is the most commonly performed transplant procedure in human medicine. Despite immune privilege, immunologic rejection represents one of the main reasons for corneal allograft failure. Immunohistologic studies showed a massive infiltration of CD3+, CD4+, CD8+ and CD68+ cells, and macrophages in rejected corneal allografts, all of which are considered to be responsible for graft rejection. The mainstay therapy of corneal rejection is the use of topical corticosteroid eye drops in the form of prednisolone acetate 1%. Because of the effect in reducing activated T cells, several recent studies have investigated the efficacy of topical ophthalmic tacrolimus in preventing corneal graft rejection. Topical tacrolimus ointment 0.03% is being evaluated as a second-line treatment in patients with high-risk corneal grafts.

Inflammatory Conjunctival and Corneal Diseases

- ***Vernal Keratoconjunctivitis (VKC):*** Though increased serum levels of total and specific IgE and the response to anti-allergic therapy are common features ascribed to VKC and to other allergic diseases, the accumulation of a large amount of immunologic data has proved that the pathogenesis of VKC is much more complex than a mere type 1 hypersensitivity reaction. In the past several years, many experimental and clinical studies about the cells and mediators involved in initiating and perpetuating the ocular allergic inflammation have shown that Th2 cells and their cytokines, corneal fibroblasts, and epithelium, along with various growth factors, play an important role in the pathogenesis of VKC.[35] Histologically, eosinophilic infiltration is seen within giant conjunctival follicles and in the limbal Trantas dot. CD4+ T cells are found abundantly in conjunctival scrapings and biopsy specimens. These CD4+ cells had been cloned and were demonstrated to exhibit Th2 phenotypes. These T-cell mediated events are likely targets of tacrolimus therapy of VKC. Tacrolimus alleviates the symptoms of and improves visual acuity with few or no adverse effects in patients with VKC.
- ***Atopic Keratoconjunctivitis (AKC):*** The pathophysiology of AKC is still unclear. It appears to develop in the setting

of atopic eyelid dermatitis, as a result of hypersensitivity reactions localized to the ocular surface or changes in eyelid function and anatomy.[36] Immunopathologic changes include invasion of the epithelium by eosinophils and mast cells, and significant infiltration of the stroma by activated T cells that produce IL-2 and interferon-g. Elevated levels of the proinflammatory cytokines, tumor necrosis factor-a and interferon-g are found in tears of AKC patients. Topical corticosteroids may improve signs and symptoms but carry a risk of complications with chronic treatment. Tacrolimus ointment appears to offer a safer option for long-term therapy of this T-cell-mediated ocular surface disorder.

- ***Atopic Blepharoconjunctivitis:*** The efficacy and safety of tacrolimus ointment on conjunctival cytology has been evaluated in a retrospective study of ten patients with severe atopic blepharoconjunctivitis or keratoconjunctivitis who were treated with 0.03% tacrolimus ointment once daily as an intermittent treatment. Marked clinical responses in blepharitis and conjunctivitis symptoms were observed after an average of 6 weeks of follow-up. A statistically significant decrease was observed in conjunctival eosinophils (decreased by 85%; p= 0.01), neutrophils (decreased by 50%; p= 0.01), and lymphocytes (decreased by 58%; p = 0.02).

- ***Intractable Allergic Conjunctivitis:*** In patients with intractable allergic conjunctivitis tacrolimus 0.03% ointment has been described. Tacrolimus 0.03% ointment is applied into the conjunctival sac of both eyes twice daily for 8 weeks, followed by a 2-week washout period. Benefits of topical tacrolimus are partially sustained for 2 weeks after termination of drug treatment, although there is a degree of clinical relapse in most cases. Blood tacrolimus levels are mostly undetectable. It has been seen that application of tacrolimus 0.03% ointment into the conjunctival sac appears to be effective and well tolerated in the treatment of allergic conjunctivitis refractory to traditional treatment.

- ***Mooren's Ulcer:*** In a retrospective, interventional, consecutive case series,[37] it was seen that compared with corticosteroid treatment, topical 0.1% tacrolimus used alone or combined with keratoplasty is an effective and well tolerated therapy for patients with recurrent Mooren's ulcer.

Uveitis

Recent studies have shown that intravitreal injection or sustained release of tacrolimus can be effective for experimental uveitis.[38] A multicenter, open, clinical trial in Japan first examined the use of tacrolimus in 53 patients with non-infectious uveitis.[18-20] Diseases such as Behcet's disease, sympathetic ophthalmia, refractory uveitis (to corticosteroids and cyclosporine), idiopathic retinal vasculitis, and sarcoidosis have been treated orally with tacrolimus.[18-20] Most uveitis symptoms improved in a dose dependent manner, with effective doses of 0.1–0.15mg/kg.[18] Severe adverse effects with tacrolimus treatment (including renal dysfunction and neurologic disorders) were observed, though these effects ceased when the drug treatment was discontinued. Therefore, tacrolimus is effective in patients with uveitis, but it is important to monitor the occurrence of adverse effects.[18-20]

Graft-Versus-Host Disease (GVHD)

GVHD is a severe and life-threatening complication of allogenic stem cell transplantation (ASCT) to treat leukemia or lymphoma. Ocular manifestations occur in about half of GVHD cases, with signs and symptoms of dry eye and meibomian gland disease being the most common.[39] In a series of 130 patients who underwent ASCT, ocular manifestations were seen in 29 (22.3%) of those with chronic or acute GVHD. They were thought to be due to infiltration of the lacrimal glands and conjunctiva with T cells and consequent inflammatory mediated dysfunction of the secretory epithelium in these tissues.

Lacrimal gland inflammation was accompanied by increased numbers of stromal fibroblasts and fibrosis. Treatments for ocular manifestations of GVHD have included systemic immunomodulators and topical corticosteroids. Ocular GVHD can be very severe and unresponsive to standard GVHD treatment. A report by Ogawa and Masataka[39] suggested that tacrolimus is effective in the treatment of chronic GVHD with ocular involvement. In another report, by Ahmad et al.,[40] of acute GVHD with extensive ocular involvement, >90% corneal epithelial defects in both eyes responded dramatically to systemic tacrolimus. To avoid the potential morbidity and mortality of long-term systemic immunosuppression, Tam et al.[16] reported the use of topical tacrolimus 0.03% ointment in the treatment of ocular surface inflammation due to chronic GVHD.

Proliferative Vitreoretinopathy (PVR)

Burak Turgut et al[41] investigated the effect of intravitreal tacrolimus on an animal model of PVR. When assessing the average PVR stages in terms of severe PVR rates, the PVR/ tacrolimus group had significantly improved when compared with the PVR/ saline group. The PVR/ tacrolimus group demonstrated significantly decreased levels of transforming growth factor-b, platelet-derived growth factor, and fibroblast growth factor when compared with the PVR/ saline group and also demonstrated significant improvement in epiretinal membrane formation and retinal fold in the presence of histopathologic levels.

The difference in degradation of photoreceptor cells between the two groups was not statistically significant. This study suggests that intravitreal tacrolimus application may suppress PVR development and that tacrolimus may merit investigation for the prophylaxis of PVR.

Glaucoma Filtering Surgery

Sermal Arslan et al.[42] investigated the effects of topically administrated tacrolimus and octreotide on modulation of postoperative scarring in experimental glaucoma filtration surgery. It was seen that topical administration of tacrolimus and octreotide effectively reduced the subconjuntival scarring 2 weeks after experimental glaucoma filtration surgery.

Conclusion

Tacrolimus is an immunosuppressant that was discovered after cyclosporine. It has a mechanism of action similar to that of cyclosporine, but is 50–100 times more potent.[32] The pharmacology of tacrolimus includes reduction of proinflammatory cytokines, activated T lymphocytes, and markers of apoptosis; it also exerts neuroprotective effects as well as inhibits the loss of conjunctival epithelium and decrease in the number of goblet cells. Many chronic ocular disorders share similar mechanisms, and the effects of tacrolimus on corneal graft, inflammatory conjunctival and corneal diseases, uveitis, and GVHD have been reported by various studies mentioned above. These chronic disorders appear to be refractory to other available treatments in many patients. As a result, the patients must rely on prolonged courses of corticosteroids, with the attendant risks of cataract formation and corticosteroid induced glaucoma. Therefore, ophthalmic tacrolimus is a welcome addition to the therapeutic armamentarium for these corneal and ocular surface diseases, particularly in light of its excellent safety profile to date.

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