

A peer look on pharmacology of two splendid immunomodulators: Spotlight on ophthalmic approach

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ABSTRACT

Tacrolimus (FK506) is a novel macrolide immunosuppressant isolated from a strain of Streptomyces and is widely used for transplantation. It has a mechanism of action similar to that of cyclosporine and is a lipophilic molecule which blocks the early phase of T-cell activation, inhibiting both T-lymphocyte signal transduction and IL-2 transcription. Clinical trials of tacrolimus has shown it to be more effective than cyclosporine in liver, kidney, and pulmonary transplantation and lesser toxic than cyclosporine. It impairs prostaglandin synthesis and the release of histamine from mast cells. Thus, it is used in treatment of immune mediated diseases, such as corneal graft rejection, ocular inflammation, and uveitis. In this article, we have reviewed Pharmacology of two chief Immunomodulators and highlightened their role in several conditions such as Keratoconjuctivitis, Graft versus Host Disease and with the special consideration of Ophthalmic uses.

Key Words: Immunomodulators, Calcineurin inhibitors, Tacrolimus, Cyclosporine, Keratoconjunctivitis

INTRODUCTION

Tacrolimus was discovered in 1987 [1] and was among the first macrolide immunosuppressants discovered, preceded by rapamycin (sirolimus)) in 1975. It is a 23-membered macrolide lactone produced by a soil bacterium, Streptomyces tsukubaensis.[2] Origin of the name tacrolimus is from 'Tsukuba macrolide immunosuppressant' [3], While cyclosporine is isolated from the fungus Tolypocladium inflatum (Beauveria nivea), found in a soil sample obtained in 1969 from Hardangervidda, Norway, by Hans Peter Frey, a Sandoz biologist.[4] Most peptides are produced by ribosomes, but cyclosporine is acyclic nonribosomal peptide of 11 amino acids and comprises of a single D-amino acid, which are seldom encountered in nature.[5]

The immunosuppressive effect of cyclosporine was discovered in 1972 by employees of Sandoz (now Novartis) in Basel, Switzerland, in a screening test on immune suppression designed and implemented by Hartmann F. Stahelin. The success of cyclosporine in preventing organ rejection was shown in kidney transplants by R.Y. Calne and colleagues at the University of Cambridge, [6] and in liver transplants performed by Thomas Starzl at the University of Pittsburgh Hospital. The first patient was a 28-year-old woman [7].

Tacrolimus (FK506) [8] is a unique macrolide immunosuppressant isolated from a strain of Streptomyces and is now used for transplantation worldwide. It has a mechanism of action like to that of cyclosporine. Clinical trials of tacrolimus in liver, kidney, and pulmonary transplantation have shown it to be more effective than cyclosporine, [9-11] and less likely to cause systemic hypertension and lipid abnormalities [9, 12-14]. Outside the field of transplantation, tacrolimus ointment [15-17] is currently available for treatment of atopic dermatitis. Tacrolimus ointment has greater efficacy adverse and lesser effects than corticosteroid ointments [18] In 1989, Kobayashi et al. [19] first assessed that tacrolimus suppressed corneal graft rejection in rabbits. Since then, the use of tacrolimus has been of special interest in ophthalmology due to its effectiveness in the treatment of immune-mediated diseases such as corneal graft rejection [20, 21] ocular inflammation [22, 23] ocular pemphigoid, [24] and uveitis [25-

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27]. Immunomodulatory drugs like cyclosporine and tacrolimus has been successfully used for treatment of moderate to severe venal keratoconjunctivitis (VKC) and in numerous conditions. There ophthalmic are studies indications of suggesting tacrolimus and cyclosporine in treatment of various ophthalmic conditions. However there are fewer studies in which comparison of tacrolimus and cyclosporine treatment for VKC in terms of efficacy and safety is demonstrated and none of the study is performed in Indian setup [28].

MECHANISM OF ACTION: TACROLIMUS AND CYCLOSPORINE

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 peptidylprolyl 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 known as FKBP-12. [29, 30] It is a lipophilic molecule which blocks the early phase of T-cell activation, thus inhibiting both Tlymphocyte signal transduction and IL-2 transcription [31]. Furthermore, it is also reported that tacrolimus inhibits the release of histamine from mast cells and impairs prostaglandin synthesis in its de novo way [32]. It also inhibits the histamine release and these three actions together may reduce allergic symptoms [33].

In medicine, the most significant effect of cyclosporine is to lessen the activity of T cells and their immune response. It binds to the cytosolic cyclophilin (immunophilin) protein of lymphocytes, especially T cells. This complex of cyclosporine and cyclophilin inhibits calcineurin, which, under normal circumstances, is responsible for activating the transcription of interleukin 2. In T-cells, activation of the T-cell receptor normally elevates intracellular calcium, which acts via calmodulin to activate calcineurin. Calcineurin then dephosphorylates the transcription factor nuclear factor of activated T-cells (NFATc), which moves to the nucleus of the T-cell and stimulates the activity of genes coding for IL-2 and related cytokines. Cyclosporine prevents the dephosphorylation of NF-AT by binding to cyclophilin [34]. It also reduces lymphokine production and interleukin release and, therefore, causes reduced function of effector T-cells. It does not affect cytostatic activity. Cyclosporine affects mitochondria by preventing the mitochondrial permeability transition pore from opening, thus inhibiting cytochrome c release, a potent apoptotic stimulation factor. This is not only the primary mechanism of action for clinical use, but is also an

important effect for research on apoptosis. Cyclosporine binds to the cyclophilin D protein (CypD) that comprises part of the mitochondrial permeability transition pore (MPTP), [35, 36] and by inhibiting the calcineurin phosphatase pathway [37,38, 39]. The MPTP is found in the mitochondrial membrane of cardiac myocytes (heart muscle cells) and moves calcium ions (Ca2+) into the mitochondria [37,39]. If unregulated, this can lead to mitochondrial swelling and dysfunction. To allow for normal contraction, intracellular Ca2+ increases, and the MPTP in turn opens, shuttling Ca2+ into the mitochondria.[40] Calcineurin is a Ca2+-activated phosphatase (enzyme that removes a phosphate group from substrate) that regulates cardiac hypertrophy [38,41,42]. Regulation occurs through NFAT (nuclear factor of activated T-cells) activation, which, when dephosphorylated, binds to GATA and causes formation of a transcription factor (protein that can bind DNA and change the expression of DNA) with ability to regulate the hypertrophic gene. Activation of calcineurin leads to hypertrophy [38,40].

PHARMACOKINETICS

Tacrolimus: Tacrolimus belongs to pregnancy category C and can only be sold on prescription basis. Routes of administration include topical, oral and intravenous. Tacrolimus is a hydrophobic molecule which means that aqueous solutions at clinically beneficial concentrations are likely to be unstable. Attempts to overcome this have lead to ophthalmic solutions were prepared using castor oil, [43] olive oil, [44] and dextrin [45]. Although burning, redness, itching and epithelial keratitis limit the use of such oil vehicles. To focus the problem of tacrolimus's limited ability to penetrate the cornea and reach effective therapeutic intraocular concentrations, several vehicles have been tested to alter its intraocular penetrability. Tacrolimus encapsulated in cyclodextrin has shown better intraocular distribution to eliminate or delay corneal allograft rejection [44] Liposome was also found effective as a carrier to deliver higher tacrolimus concentrations into all ocular tissues compared with olive oil [44] 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. Bioavailability on oral administration is 20% less after eating food rich in fat. ~99% bound to human plasma protein, primarily to albumin and alpha-1acid glycoprotein. Protein binding range from 75-99% and is metabolized by hepatic cytochromes CYP3A4, CYP3A5. Biological half-life is 11.3 hrs (range 3.5-40.6h) and excretion is mainly faecal.

Cyclosporine: Cyclosporine belongs to pregnancy category C and can only be sold on prescription basis. Routes of administration include oral, intravenous and topical route (ophthalmic). Metabolised mainly by hepatic enzymes CYP3A4 and biological half-life is upto 24 hrs, excretion is mainly by biliary route [45].

SYSTEMIC INDICATIONS:

Tacrolimus as an Immunosuppressant 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 [47]. 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 tacrolimus pharmacokinetics of between individuals make it hard to predict what drug concentration will be achieved with a particular dose or dosage range [48] Orally administered tacrolimus is also used for treatment of rheumatoid arthritis, [49] moderate to severe psoriasis, [50] and inflammatory bowel disease, [51] 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, [20] as well as for severe ocular inflammatory conditions such as uveitis [20-27] and Behcet's disease. Daily doses of 1-2 mg/day are used for ocular inflammatory conditions

Reduction of pro-inflammatory 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 [8]. 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 intra cellularly, 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 [52]. 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 increased expression notion that 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

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antirejection effects of tacrolimus may be partly

due to blockade of CD40 VCD154 interaction.

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.

Keratoconjunctivitis (VKC): Though Vernal 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 [53] 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.

(AKC):-Atopic Keratoconjunctivitis The pathophysiology of AKC is still unclear. It appears to develop in the setting reactions localized to the ocular surface or changes in eyelid function and anatomy [54]. 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 proinflamatory 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) [55].

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 2week 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, [56] 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 [57]. A multicenter, open, clinical trial in Japan first examined the use of tacrolimus in 53 patients with non-infectious uveitis [25-27]. 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 [25-27]. Most uveitis symptoms improved in a dose dependent manner, with effective doses of 0.1-0.15mg/kg [23]. 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 [25-27].

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 [58]. In a series of 130 ASCT, patients who underwent 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 [58] suggested that tacrolimus is effective in the treatment of chronic GVHD with ocular involvement. In another report, by Ahmad et al. [59] 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. [23] 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 [60] 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 studv 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. [61] investigated the effects of topically administrated tacrolimus and octreotide on of postoperative modulation 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.

Cyclosporine as an Immunosuppressant and Immunomodulator

Medical uses: Cyclosporine is approved by the FDA to prevent and treat graft-versus-host disease in bone-marrow transplantation and to prevent rejection of kidney, heart, and liver transplants [62, 46] It is also approved in the US for the treatment of rheumatoid arthritis and psoriasis, [46] as an ophthalmic emulsion for the treatment of dry eyes [64] and as a treatment for persistent nummular keratitis following adenoviral keratoconjunctivitis

[65] In addition to these indications, cyclosporine is also used in severe atopic dermatitis, Kimura disease, pyoderma gangrenosum, chronic autoimmune urticaria, acute systemic mastocytosis, and, infrequently, in rheumatoid arthritis and related diseases, although it is only used in severe cases.

It has also been used to help treat patients with acute severe ulcerative colitis that do not respond to treatment with steroids [66]. This drug is also used as a treatment of posterior or intermediate uveitis with non-infective etiology and is sometimes prescribed in veterinary cases, particularly in extreme cases of immune-mediated hemolytic anemia [67].

Neuroprotection: Cyclosporine is currently in a phaseII/III (adaptive) clinical study in Europe to determine its ability to ameliorate neuronal cellular damage and reperfusion injury (phase III) in traumatic brain injury. This multi-center study is being organized by Neuro Vive Pharma and the European Brain Injury Consortium using Neuro Vive's formulation of cyclosporine called NeuroSTAT (also known by its cardioprotection trade name of CicloMulsion). This formulation uses a lipid emulsion base instead of cremophor and ethanol [68] NeuroSTAT was recently compared to Sandimmune in a phase I study and found to be bioequivalent. In this study, NeuroSTAT did not exhibit the anaphylactic and hypersensitivity reactions found in cremophor- and ethanol-based products [69]. Cyclosporine has been investigated as a possible neuroprotective agent in conditions such as traumatic brain injury, and has been shown in animal experiments to reduce brain damage associated with injury [70] Ciclosporin blocks the formation of the mitochondrial permeability transition pore, which has been found to cause much of the damage associated with head injury and neurodegenerative diseases. Cyclosporine's neuroprotective properties were first discovered in the early 1990s when two researchers (Eskil Elmér Hiroyuki Uchino) and were conducting experiments in cell transplantation. An unintended finding was that CsA was strongly neuroprotective when it crossed the blood-brain barrier [71] The same process of mitochondrial destruction through the opening of the MPT pore is implicated in making traumatic brain injuries much worse [72].

Cardiac disease: Cyclosporine has been used experimentally to treat cardiac hypertrophy [37, 41] (an increase in cell volume). Inappropriate opening of the mitochondrial permeability transition pore (MPTP) manifests in ischemia [37] (blood flow restriction to tissue) and reperfusion injury [35] (damage occurring after ischemia when blood flow

returns to tissue), after myocardial infarction [38] (heart attack) and when mutations in mitochondrial DNA polymerase occur [37] The heart attempts to compensate for disease state by increasing the intracellular Ca2+ to increase the contractility cycling rates [40]. Constitutively high levels of mitochondrial Ca2+ cause inappropriate MPTP opening leading to a decrease in the cardiac range of function, leading to cardiac hypertrophy as an attempt to compensate for the problem [38, 40]. CsA has been shown to decrease cardiac hypertrophy by affecting cardiac myocytes in many ways. CsA binds to cyclophilin D to block the opening of MPTP, and thus decreases the release of protein cytochrome C, which can cause programmed cell death [37, 40, 63]. CypD is a protein within the MPTP that acts as a gate; binding by CsA decreases the amount of inappropriate opening of MPTP, which decreases the intramitochondrial Ca2+ [40] Decreasing intramitochondrial Ca2+ allows for reversal of cardiac hypertrophy caused in the original cardiac response [40]. Decreasing the release of cytochrome C caused decreased cell death during injury and disease [37]. CsA also inhibits the phosphatase calcineurin pathway. Inhibition of this pathway has been shown to decrease myocardial hypertrophy [41, 42]

ADVERSE EFFECTS

From oral and intravenous administration: Side effects can be severe and include infection, cardiac damage, hypertension, blurred vision, liver and kidney problems (tacrolimus nephrotoxicity), [73] hyperkalemia, hypomagnesemia, hyperglycemia, diabetes mellitus, itching, lung damage (sirolimus also causes lung damage),[74] and various neuropsychiatric problems such as loss of appetite, insomnia, posterior reversible encephalopathy confusion, weakness, depression, syndrome, cramps, neuropathy, seizures, tremors, and catatonia [75]. In addition, it may potentially increase the severity of existing fungal or infectious conditions such as herpes zoster or polyoma viral infections.

Carcinogenesis and mutagenesis: In people receiving immunosuppressants to reduce transplant graft rejection, an increase risk of malignancy is a recognized complication. The most common cancers are non-Hodgkin's lymphoma and skin cancers. The risk appears to be related to the intensity and duration of treatment.

From topical use: The most common adverse events associated with the use of topical tacrolimus ointments, especially if used over a wide area, include a burning or itching sensation on the initial

applications, with increased sensitivity to sunlight and heat on the affected areas. Less common are flu-like symptoms, headache, cough, and burning eyes [76]. The use of topical tacrolimus ointments should be avoided on known or suspected malignant lesions. The use of tacrolimus on patients with Netherton's syndrome or similar skin diseases is not recommended. Patients should minimize or avoid natural or artificial sunlight exposure. Skin infections should be cleared prior to application, and the risk of certain skin infections may be increased. Tacrolimus should not be used with occlusive dressings.

Contraindications and Precautions: Breastfeeding, Hepatic disease, Immunosuppression, Infants, Infection, Intravenous administration, neoplastic disease, such as: Skin cancer, Lung cancer, Occlusive dressing, Oliguria, Pregnancy, QT interval prolongation, Sunlight (UV) exposure and Grapefruit juice [77]. Most frequent side effect seen with cyclosporine treatment is burning sensation soon after instillation of eye drops and is reported in almost all studies done. Tacrolimus is associated with transient ocular irritation commonly [78]. Other serious adverse drug reactions (ADRs) include gingival hyperplasia, convulsions, peptic ulcers, pancreatitis, fever, vomiting, diarrhea, confusion, hypercholestolemia, dyspnea, numbness and tingling particularly of the lips, pruritus, high blood pressure, potassium retention possibly leading to kidney and liver dysfunction (nephrotoxicity and hepatotoxicity), burning sensations at finger tips, and an increased vulnerability to opportunistic fungal and viral infections. In short, it is nephrotoxic, neurotoxic, causes hypertension (due to renal vasoconstriction and increased sodium reabsorption), and increases the risk of squamous cell carcinoma and infections. It also causes gingival hypertrophy and hirsutism which is not seen with tacrolimus.

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 [44] The pharmacology of tacrolimus comprises reduction of proinflammatory cytokines, activated T lymphocytes, and markers of apoptosis; it also exerts neuroprotective effects as well as obstructs the loss of conjunctival epithelium and reduction in the number of goblet cells. Many chronic ocular disorders assign similar mechanisms, and the effects of tacrolimus on corneal graft, inflammatory conjunctival and corneal diseases, uveitis, and GVHD have been established by various studies mentioned above. These chronic disorders appear to be intractable to

other existing treatments in many patients. As a result, the patients must depend on prolonged courses of corticosteroids, with the attendant risks of cataract formation and corticosteroid induced glaucoma. Consequently, ophthalmic tacrolimus is a welcome addition to the therapeutic armamentarium for these corneal and ocular surface diseases, particularly in importance of its excellent safety profile to date.

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