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Topical tacrolimus nanoemulsion, a promising therapeutic approach for uveitis

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ABSTRACT

Uveitis is a sight threatening inflammatory disorder that affects all ages and remains a significant cause of visual loss. Inflammatory activity plays an important role in the whole pathogenesis of uveitis. Treatment of uveitis is mainly driven by corticosteroids that have potential side effects. Recent investigations demonstrated that tacrolimus inhibits T-cell proliferation and suppresses release of inflammatory cytokines. Since tacrolimus is a definite immunosuppressive agent, and since inflammatory process has been involved in uveitis, the compound must have effect on the progression of uveitis through reduction in inflammatory activity. Even results of the clinical trials demonstrate that tacrolimus have useful role in treatment of sight threatening uveitis that is refractory to other therapy. Studies also indicate that long term use of tacrolimus is well tolerated. However, its use in uveitis is limited because of its poor physico-chemical properties including poor aqueous solubility and high molecular weight (822 Da). Therefore, we have proposed that tacrolimus nanoemulsion administered topically is a promising therapeutic approach to treat uveitis. Based on previous evidences, we have hypothesized that nanoemulsion formulation of tacrolimus can improve efficacy and safety profile of tacrolimus.

Introduction

Uveitis is an umbrella term used to describe a wide array of inflammatory conditions occurring inside the eye. The term literally means inflammation of the uvea (vascular, pigmented middle coat of the eyewall) composed of the iris, ciliary body and the choroid, however, adjacent structures such as the sclera, retina and optic nerve may also be involved [1–3]. Uveitis is the third leading cause of blindness and accounts for 5–20% of blindness in the developed world and about 25% of blindness in the developing world [1–3]. Uveitis is a sight threatening inflammatory disorder that affects all ages and remains a significant cause of visual loss [3].

Uveitis is a common occurring disease resulting from a wide variety of infectious, immunogenic and traumatic insults. Whatever the cause may be, the inflammatory process is the mainstay in the development and progression of uveitis [4]. Tacrolimus is a novel, nonsteroidal, macrolide immunomodulator used for transplantation worldwide [5]. Outside the field of transplantation, tacrolimus is available for treatment of atopic dermatitis [6]. Backed by potent immunosuppressive effect and lipophilic nature, tacrolimus is expected to exhibit excellent therapeutic efficacy in suppressing immune responses related to inflammatory ocular diseases [7,8]. The use of tacrolimus in the management of uveitis is fail-safe because tacrolimus is shown to suppress entire pathogenetic pathway of uveitis [7,8]. Tacrolimus inhibit expression of TLRs, T-cell proliferation, release of inflammatory cytokines such as IL-1, IL-6, IL-23, TNF-α and IFN-γ, and adhesion molecules, all of which are implicated in the development of uveitis [8–10].

Tacrolimus was shown to be effective in patients with refractory uveitis through oral [11] or intravitreal administration [12]. Its use is limited because of likelihood of severe adverse effects including nephrotoxicity upon repeated oral administration [13] and local complications upon repeated intraocular injections [14]. To improve the safety profile topical application is preferred. Long term safety profile and ocular tolerance of topical tacrolimus is well established [13]. However, poor physico-chemical properties of tacrolimus limit its intraocular penetration following topical administration [15]. Thus, improvement of ocular bioavailability of tacrolimus using efficient ocular carrier would be beneficial for the treatment of uveitis after topical administration of tacrolimus [16,17]. Thus, we suppose that tacrolimus nanoemulsions could be a promising therapy for treatment of uveitis.

Pathogenesis of uveitis

Uveitis is believed to have an autoimmune component supported by lack of known infectious triggers and by frequent pres-

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ence of immunological responses. The innate immune system uses a variety of pattern recognition receptors (PRRs) that are either expressed on the cell surface (toll like receptors (TLRs) and phagocytic C-type lectin receptors), or expressed intracellularly (nucleotide oligomerisation domain (NOD) proteins), or secreted pattern recognition molecules (mannan binding lectins) [18]. Recently, TLRs have emerged as a key component of the immune system that detects microbial infection and/or innate (environmental) stimuli and triggers inflammation [19]. Several in vitro and in vivo studies have demonstrated the expression and function of TLRs in the eye particularly in sclera, uvea and retina, raising the possibility that their inhibition is a promising approach for treatment of inflammation in uveitis [19]. Recognition of antigen (Ag, pathogen-associated molecular patterns present on the surface of microorganisms but not host tissues) by TLRs results in:

(1) Activation of antigen presenting cells (APC, TLR-expressing cells) such as dendritic cells (DC) and macrophages. TLR mediated activation of DCs induces the production of proinflammatory cytokines, upregulation of co-stimulatory and major histocompatibility complex (MHC) molecules, and thereby enhances the antigen presenting capacity of DCs. This leads to activation, differentiation and clonal expansion of antigen specific T cells, triggering the adaptive arm of the immune response. The effector T-cells extravagate in eyes, influences differentiation of type 1 (Th1) and type 17 (Th17) T helper cells which initiates a rapid inflammatory response resulting in uveitis. The role of T-cell activation, IL-$_{12}$ and IFN-γ producing Th1 and IL-$_{23}$ producing Th17 in the pathogenesis of uveitis has been well understood and these mediators represent therapeutic targets for treatment of uveitis [10].
(2) Dimerisation of TLRs, which through the activation of signaling pathways, triggers the activation of the transcription factor, nuclear factor κB (NF-κB). NF-κB activation induces the expression of various proinflammatory cytokines, chemokines, adhesion molecules, and proinflammatory mediators. In addition to IL-$_{12}$ and IL-$_{23}$, which are produced by APC and are key proinflammatory mediators of Th1 or Th17 responses, IL-$_1$, IL-$_6$, and TNF-α are major proinflammatory cytokines produced by various cell types, including lymphocytes, monocyte/macrophages, DC and ocular resident cells. These cytokines play central role during inflammation and thus, are potential targets for treatment of uveitis [10].

Uveitis, if untreated progresses to vision threatening vasculitis and necrosis. Cytokines along with effector T-cells play major role in pathogenesis of vasculitis and necrosis. They extravagate into the eye and contribute to the breakdown of the blood–retinal barrier, possibly through opening of tight junctions and increased vesicular transport within the endothelial cells [10,20]. Further, activation of neutrophils and formation of reactive oxygen species, immune complexes and release of tissue-destructive matrix metalloproteinases causes vasculitis and necrosis. Thus, cytokines and effector T-cells are promising targets to control progression of uveitis [20].

Inflammatory response by inflammatory mediators such as TLRs, effector T-cells, IL-$_1$, IL-$_6$, IL-$_{12}$, IL-$_{23}$ and TNF-α, plays an important role in the onset, progression and pathogenesis of uveitis. Suppression of inflammation by inhibition of expression and proliferation of these mediators is regarded as a key approach to treat uveitis.

Tacrolimus role in uveitis

Treatment of uveitis is mainly driven by systemic, topical or intraocular corticosteroids, which potentially have undesirable side effects including steroid-induced glaucoma, cataract formation and super-infection [21]. The therapy is typically individualized and requires regular monitoring. These problems often limit long-term steroid use for treating inflammatory ocular surface diseases [21]. Therefore, it is necessary to develop alternative nonsteroidal therapeutic modalities that have more potent anti-inflammatory actions with fewer side effects than steroids.

The efficacy of a topical nonsteroidal immunomodulator, cyclosporine, against inflammatory ocular diseases has been documented by many investigators [22]. However, high-concentration cyclosporine in oil-based formulations results in intense stinging sensation and blurred vision upon instillation, leading to poor compliance. In addition to this, systemic and localized ocular toxicity associated with high-concentration cyclosporine is also a concern [23]. Studies also demonstrated that cyclosporine has failed to exhibit sufficient clinical efficacy in some steroid-dependent cases [24]. Tacrolimus (FK506) is a novel, nonsteroidal, macrolide immunomodulator having mechanism of action similar to that of cyclosporine. However, it is 10–50 times more potent than cyclosporine [8,24]. Clinical studies have shown that tacrolimus is more effective than cyclosporine at lower concentrations [24]. Due to improved potency, tacrolimus exhibit superior safety profile and, unlike cyclosporine, it does not induce systemic hypertension and lipid abnormalities [13].

Tacrolimus is isolated from *Streptomyces tsukubaensis* by the exploratory research laboratories of Fujisawa Pharmaceutical Co., Ltd (Osaka, Japan), and is now used for transplantation worldwide [8]. Outside the field of transplantation, tacrolimus is currently available, as an ointment, for treatment of atopic dermatitis in US, Canada and Japan and has exhibited higher efficacy and fewer side effects than corticosteroids [6]. Tacrolimus binds in the T cells to a cellular receptor, the FK-binding protein (FKBP-12). The tacrolimus–FKBP complex then binds to and inhibits calcineurin, which in turn leads to inhibition of dephosphorylation and nuclear translocation of a cytosolic transcription factor, the nuclear factor of activated T-cell protein [8,25]. This cascade blocks the production of cytokines such as IL-$_1$, IL-$_6$, IL-$_{23}$, TNF-α and IFN-γ and this leads to inhibition of Th1 and Th2 cell activation [8,25]. Because of its potent immunosuppressive effect and lipophilic nature, topical tacrolimus is expected to exhibit excellent therapeutic efficacy in suppressing abnormal immune responses related to inflammatory ocular diseases. Based on the efficacy of tacrolimus ointment in treating atopic dermatitis [6], it has been successfully used for various immune-mediated ocular surface disorders [7]. In the field of ophthalmology, a number of studies have reported the effect of topical tacrolimus ranging from 0.03% to 0.1%, for treating inflammatory diseases of ocular surface such as conjunctivitis [26], keratoconjunctivitis [27,28], corneal graft [7], graft-vs-host disease (GVHD) [7] and penetrating keratoplasty [7,26].

Recent studies demonstrated the use of oral or intravitreal tacrolimus in the treatment of refractory uveitis with significant improvement in visual acuity [29,30]. Intravitreal injection of tacrolimus up-regulates the gene expression of neuroprotection-related molecules as well as decreases the expression of inflammatory responses related genes. These data support the notion that tacrolimus may play a potential role in retinal protection of the eyes with ongoing ocular inflammation as well as in immune regulation [29]. Along with potent anti-inflammatory action, tacrolimus exerts neuroprotective effects and reduces markers of apoptosis preventing vasculitis and necrosis associated with uveitis [7]. Interestingly, recent studies related to treatment of atopic dermatitis revealed that tacrolimus, but not cyclosporine and corticosteroids, are able to suppress expression of TLRs [31]. These results are now gaining increasing attention since TLR suppression by tacrolimus can be beneficial in treatment of uveitis because of plausible role of TLR in pathogenesis of uveitis and because of their prevalence in uvea [18,19].