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EDITORIAL

Topical biological agents targeting cytokines for the treatment of dry eye disease

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Abstract

Because inflammation plays a key role in the pathogenesis of dry eye disease and Sjögren's syndrome, topical anti-inflammatory agents such as corticosteroids and cyclosporine A have been used to treat inflammation of the ocular surface and lacrimal gland. Systemic biological agents that target specific immune molecules or cells such as tumor necrosis factor (TNF)-α, interferone-α, interleukin (IL)-1, IL-6, or B cells have been used in an attempt to treat Sjögren's syndrome. However, the efficacy of systemic biological agents, other than B-cell targeting agents, has not yet been confirmed in Sjögren's syndrome. Several studies have recently evaluated the efficacy of topical administration of biological agents targeting cytokines in the treatment of dry eye disease. Topical blockade of IL-1 by using IL-1 receptor antagonist could ameliorate clinical signs and inflammation of experimental dry eye. Using a mouse model of desiccating stress-induced dry eye, we have demonstrated that topical application of a TNF-α blocking agent, infliximab, could improve tear production and ocular surface irregularity, decrease inflammatory cytokines and Th-1 CD4+ cells on the ocular surface, and increase goblet cell density in the conjunctiva. Although controversy still remains, the use of topical biological agents targeting inflammatory cytokines may be a promising therapy for human dry eye disease.

Key words: Dry eye disease; Sjögren's syndrome; Biological agent; Tumor necrosis factor-α; Interleukin-1; B cell; Cytokine

Core tip: Although the debate remains about the efficacy of systemic biological agents on Sjögren's syndrome, topical biological agents targeting inflammatory cytokines can be applicable for the treatment of dry eye disease.

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INTRODUCTION

It is well known that tear film hyperosmolarity activates inflammation of the ocular surface, resulting in dry eye disease. Increased expression of inflammatory cytokines, chemokines, matrix metalloproteinases, apoptotic markers, CD4+ Th-1 cells, and Th-17 cells on the ocular surface and in the lacrimal gland have been demonstrated in clinical and experimental dry eye studies[1-15]. Current treatments for dry eye include artificial tears, topical anti-inflammatory agents including corticosteroids and cyclosporine A, punctal plugs, and contact lenses[16-21]. As biological products, variants of serum and plasma, such as autologous serum, umbilical cord serum, and platelet-rich plasma, can also be used topically in severe dry eye[22-25]. Despite these treatments, patients with severe dry eye or

Sjögren's syndrome still complain of discomfort and have signs of persistent inflammation on the ocular surface.

SYSTEMIC BIOLOGICAL AGENTS

Systemic biological agents that target specific immune molecules or cells have been used in an attempt to treat autoimmune diseases such as Sjögren's syndrome. These targets include tumor necrosis factor (TNF)-α, interferone (IFN)-α, interleukin (IL)-1, IL-6, and B cells[26-29].

Although anti-TNF-α agents were found to be successful in modulating other autoimmune diseases, such as rheumatoid arthritis, controversy exists regarding the efficacy of systemic TNF-α blocking agents in Sjögren's syndrome. In a study using a rabbit model of dacryoadenitis, the transfer of a TNF-α inhibitor gene suppressed the appearance of Sjögren's syndrome-like features including reduced tear production and lacrimal gland immunopathology[30]. However, TNF-α inhibitors had no therapeutic effect in an autoimmune murine model of Sjögren's syndrome[31]. In clinical studies, application of a anti-TNF-α agent, infliximab, caused a rapid and sustained improvement in symptoms and signs without any major adverse reaction, whereas it did not show a therapeutic response in patients with primary Sjögren's syndrome compared with controls[32,33]. In addition, oral or subcutaneous administration of etanercept was ineffective in Sjögren's syndrome patients[34,35].

Oral administration of low dose IFN-α showed inconsistent efficacy in various studies but failed to achieve the primary endpoint in a randomized controlled trial[27,36-38]. The efficacy of IL-1 and IL-6 and other cytokines in Sjögren's syndrome is still under investigation[28,29].

In contrast, systemic B-cell targeted therapy has shown clinically promising results in patients with Sjögren's syndrome. Several controlled trials demonstrated considerable improvements in sicca features, salivary flow, ocular surface staining by lissamine green, fatigue, extraglandular manifestations, and quality of life scores after treatment with the B-cell-depleting anti-CD20 antibody, rituximab[39,40]. Although the marked inflammatory infiltrate in the affected glands includes a high percentage of T cell, there is abundant evidence that B cell hyperactivity is a main pathogenic factor in Sjögren's syndrome[41]. Administration of the anti-CD22 antibody, epratuzumab, also showed marked improvements in fatigue and subjective outcomes in patients with Sjögren's syndrome[42]. The B-cell-activating factor (BAFF), which stimulates the production of antibodies by B cells, may be another target for therapy.

TOPICAL BIOLOGICAL AGENTS

Among many targets including cytokines, cytokine signaling pathways, and cell adhesion or leukocyte trafficking, cytokines are the most commonly used therapeutic target for Sjögren's syndrome and inflammatory dry eye. Compared with systemic biological agents for Sjögren's syndrome, only a few studies have evaluated the efficacy of topical administration of biological agents that block pro-inflammatory cytokines in the treatment of dry eyes. Okanobo *et al*[43] demonstrated the therapeutic efficacy of topical blockade of IL-1 in the treatment of experimental dry eye disease. According to their study, application of topical formulations containing 5%IL-1 receptor antagonist (IL-1Ra) was effective in reducing clinical signs and inflammation of dry eye, as evidenced by a decrease in corneal fluorescein staining, the number of central corneal CD11b+ cells, corneal lymphatic growth, and corneal IL-1β expression[43]. The effects by topical IL-1Ra were comparable with those by topical methylprednisolone.

We previously investigated the effects of topical infliximab on the tear film and ocular surface of desiccating stress-induced murine dry eye[44]. Our results showed that mice treated with 0.01% or 0.1% infliximab eye drops had a significant improvement in tear production and corneal surface irregularity. Treated mice also had lower levels of inflammatory cytokines (IL-1β, IL-6, IL-17, IFN-γ, and TNF-α) and Th-1 CD4+ cells and higher goblet cell density in the conjunctiva compared with controls. The reason why the topical anti-TNF-α agent was effective in ocular surface inflammation in contrast to systemic agents could be explained by the dual effect of anti-TNF-α which can enhance T cell receptor-mediated Th1 and Th17 cell activation in peripheral blood and prevent the migration of pathogenic T cells to inflamed tissues, thereby inhibiting inflammation in target tissues[45]. The topical administration of TNF-α blocking agents may be effective in treating dry eye by affecting the inflamed ocular surface directly[44].

Recently, we have reported the therapeutic effect of topical adiponectin, a protein secreted by the adipose tissue, in a mouse model of experimental dry eye[46]. Adiponectin is known to have anti-inflammatory effects as well as anti-diabetic, anti-atherogenic, and anti-angiogenic properties[47-50]. The globular region of adiponectin is structurally similar to TNF-α. Adiponectin can inhibit TNF-α and TNF-α-mediated activation of nuclear factor-κB[51,52]. It can activate adenosine monophosphate-activated protein kinase and protect salivary gland epithelial cells from spontaneous and IFN-γ-induced apoptosis in autoimmune inflammation[53]. CD4+ T-cell-produced IFN-γ plays a pivotal role in Sjögren's syndrome-like conjuntival epithelial apoptosis *via* activation of the extrinsic apoptotic pathway[54]. Our study suggest that topical application of 0.001% or 0.01% globular adiponectin could improve tear production and corneal surface irregularity, decrease levels of inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ, and CXCL9) and Th-1 CD4+ cells in the conjunctiva and lacrimal gland, and could increase conjunctival goblet cell density.

Our experiments show that topical application of a TNF-α blocking agent can improve the tear film and ocular surface parameters by inhibiting inflammatory cytokines, chemokines, and T cells in the conjunctiva and lacrimal glands, and could therefore be useful in the treatment of dry eye disease. Other candidate cytokines

like IL-12, IL-17, and IL-23 may provide promising targets for Sjögren's syndrome. In addition, considering the favorable results of systemic B-cell targeted therapy observed in patients with Sjögren's syndrome, topical B-cell targeting agents such as BAFF could potentially be used as a treatment for autoimmune and inflammatory dry eye.

CONCLUSION

Although some debate still remains about the effect of systemic biological agents on Sjögren's syndrome, topical biological agents that target various inflammatory cytokines can be applicable for the treatment of human dry eye disease. Clinical studies on the safety and efficacy of topical biological agents targeting cytokines in patients with dry eye disease will be needed in the near future.

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