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Dacryology Update

Recent developments on dry eye disease treatment compounds

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Abstract

Dry eye syndrome is a common tears and ocular surface multifactorial disease, described by changes in the ocular surface epithelia related to reduced tears quantity and ocular surface sensitivity, leading to inflammatory reaction. Managing the eye inflammation proved helpful to patients with dry eye disease and current treatment is based on the use of topically applied artificial tear products/lubricants, tear retention management, stimulation of tear secretion and using anti-inflammatory drugs. In this article we revise the corresponding literature and patents assembling the new treatment approaches of novel and future pharmaceutical compounds destined for the dry eye disease treatment. The most frequent categories of compounds presented are secretagogues and anti-inflammatory drugs. These compounds are the research outcome of novel therapeutic strategies designed to reduce key inflammatory pathways and restore healthy tear film.

Keywords: Dry eye, Anti-inflammatory, Keratoconjunctivitis sicca, Keratitis sicca, Xerophthalmia, Mucin secretion, Tear secretion, NSAID

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Introduction

Dry eye is a disease which starts with unpleasant levels of symptoms of dryness of eyes and an uncomfortable feeling, greatly preventing people from performing daily activities when the disease worsens. The number of dry eye patients is increasing yearly in association with the aging of the society and the increase in VDT (video display terminal) works with personal computers and devices. Dry eye prevalence in 2009 in Spain was 11.0% among adults. Dry eye was found to be more frequent in women (11.9%) than in men (9.0%), and was significantly associated with aging.[1] Although exact etiopathogenesis of dry eye is not known, it is believed that decrease in the tear volume on the corneal and conjunctival surface caused by either a decreased tear secretion or accelerated evaporation plays the main role. The clinical features of dry eyes include ocular discomfort, feeling of dryness, feeling of eye fatigue, hyperemia, keratoconjunctival epithelial disorders and abnormalities of vision. If these symptoms and observations progress, eventually abnormality occurs in vision. Therefore, it is quite important to treat dry eye properly at an early stage. Wetness of the ocular surface and other exposed mucosae is maintained by a continuous aqueous fluid secretion produced by exocrine glands.[2–4] In the eye, basal tear flow is adjusted to variations in environmental conditions and blinking rate. Tear flow occurring in the absence of emotional or exogenous irritant stimuli ('basal' tear secretion) is adjusted to variations in environmental conditions and blinking rate.[5] Tearing also increases markedly upon ocular surface irritation.[6] Irritating stimuli are detected by mechano-nociceptor and polymodal-nociceptor trigeminal nerve endings sensitive to injurious mechanical forces, noxious heat and irritant chemicals, that evoke pain and irritation-induced tearing.[7] However, the neural structures responsible for sensing ocular surface dryness to regulate basal tearing rate remain undefined. Dry eye syndrome is a disease

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characterized by persistent dryness of the conjunctiva and opacity of the cornea. Multiple causes can lead to dry eye, which is more common in elderly people. Among diseases causing dry eye are: vitamin A deficit, Sjögren's syndrome, rheumatoid arthritis and other rheumatologic diseases, chemical or thermal burns, drugs such as atenolol, chlorpheniramine, hydrochlorothiazide, isotretinoin, ketorolac, ketotifen, levocabastin, levofloxacin, oxybutynin, and tolterodine.

Current dry eye treatment

The symptomatic relief of dry eye includes tear supplements called ''artificial tears'' which are artificial lubricants, characterized by hypotonic or isotonic buffered solutions containing electrolytes, surfactants and various types of viscosity agents.[8] Another treatment option is the application of tear retention devices. Implants are developed to permanently occlude the lacrimal puncta. These kinds of implants also known as punctal plugs, and could be absorbables and non-absorbables.[9] Additional treatment is by using moisture chamber spectacles. It has been reported that increases in periocular humidity can cause a growth of the lipid layer tear film thickness and also that spectacle wearers with dry eye have a longer inter-blink interval than those who do not wear spectacles.[10] On the pharmacology side current treatment is mainly focusing on addressing inflammation and tear restoration.[11] Dry eye disease is the outcome of many factors resulting in inflammation of the cornea and conjunctiva. The dysfunction of the tear secretory glands leads to changes in tear composition such as hyper-osmolarity which stimulates the production of inflammatory mediators on the ocular surface. This inflammation can be initiated either by chronic irritative stress like contact lens wearing or a systemic inflammatory autoimmune disease like rheumatoid arthritis.[12,13] Anti-inflammatory drugs are widely used for the treatment of the inflammation produced by the disease with the topical corticosteroid drops being the most common therapy. Corticosteroids can rapidly and effectively relieve the symptoms and signs of moderate or severe dry eye.[14] Steroids on the other hand produce severe side effects after prolonged use. The effects include risk of bacterial or fungal infection, elevated intraocular pressure and cataract formation, therefore steroids are typically used only for one to two weeks in dry eye patients.[15] As a consequence, non-steroidal anti-inflammatory drugs (NSAID) are increasingly used as dry eye treatment instead of steroids because of their non-severe side effects and because steroids locally suppress the immune response in patients with an already compromised ocular surface. The NSAIDs acutely decrease the eye discomfort due to its analgesic effect and furthermore is reducing the inflammation. In 2002 U.S. Food and Drug Administration approved the drug RESTASIS® of the company Allergan as the first prescription medicine helping to increase tear production reduced by inflammation due to chronic dry eye disease. Topical RESTASIS® diquafosol tetrasodium is an ophthalmic emulsion containing cyclosporine 0.05%.[16] Other type of drug used is the antibiotics including oral doxycycline, azithromycin, and tetracycline. There is some research on the use of serum tears and intense pulse light treatment.[17]

In this review we are presenting the trends on the oncoming treatments, analyzing the patents filled from the research institutions. The data are represented on a table of drugs and properties (Table 1).

Recent developments

Cytokine receptor inhibitors

Cytokines are a group of hormones incapable to penetrate through the cell membrane and functioning by binding to cognate receptor proteins.[18] Cytokines use multiple signaling pathways with JAK-STAT pathway being the most important. Janus kinases (JAKs) are components of the cytokine receptor signaling pathway and signal transducers and activators of transcription (STATs). After the discovery of JAK's it was identified as the STAT family of transcription factors (STAT1-5a, 5b and 6).[19] The activation of the cytokine receptor JAK signaling complex leads to the stimulation of JAK kinases resulting in the phosphorylation of receptor chains, creating docking sites for STAT transcription factors.[20] Generally, cytokine receptors do not have intrinsic tyrosine kinase activity, and thus require receptor-associated kinases to propagate a phosphorylation cascade. Cytokines bind to their receptors, causing receptor dimerization, and this enables JAKs to phosphorylate each other as well as specific tyrosine motifs within the cytokine receptors. STATs that recognize these phosphortyrosine motifs are recruited to the receptor, and after this they are activated by a JAK-dependent tyrosine phosphorylation event. Upon activation, STATs dissociate from the receptors, dimerize, and translocate to the nucleus to bind to specific DNA sites and alter transcription.[21] Small molecules acting as JAK inhibitors are already accepted as pharmaceutical solutions for a variety of autoimmune diseases.[22] Among the cytokines the most prominent family is the group of interleukins from IL-1 to IL-36. They function in immune response in charge of the defense against extracellular infections and contributing to the pathogenesis of some autoimmune inflammatory diseases among them is the dry eye disease.[23–25] Cytokines, given their central role in the pathogenesis of dry eye, are attractive targets for treatment and a significant part of pharmacology research is based on their use as anti-inflammatory agents. Eleven Biotherapeutics, Inc., is using IL-17 family cytokine compositions as antagonists. The company is evaluating the proteins of interest in a mouse model for dry eye disease. The dry eye can be induced in mice by subcutaneous injection of scopolamine and afterward the mice are placed in controlled-environment chambers.[26] This method concerns binding proteins, including non-naturally occurring and recombinantly modified proteins that bind to an IL-17R and including proteins having a mutated IL-17 cytokine sequence (patent WO/2011/044563).[27] Additionally the company is studying methods of administering an IL-1 or IL-17 cytokine for treating dry eye disorder. The antagonists can be administered topically using an ophthalmic composition to the eye prior to sleep or nocturnal rest (patent WO/2011/163452).[28] As a result of this research Eleven Biotherapeutics, designed and engineered a novel and differentiated protein-based bio-therapeutic for dry eye disease, called EBI-005, which is the first IL-1 signaling inhibitor and is designed for topical ocular administration. The company commenced Phase 1b/2a clinical trials (ClinicalTrials.gov Identifier: NCT01748578) and presented the results at the 7th international conference

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