



Current options and emerging therapies for anterior ocular inflammatory disease

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Purpose of review

Ophthalmic disorders are highly prevalent in the United States, with approximately 3.5 million individuals aged at least 40 either blind or having impaired vision. This article reviews the current leading agents and pipeline therapies for the treatment of anterior ocular inflammatory disease (AOID).

Recent findings

There has been great progress in the understanding of ocular pathophysiology in recent years. Although current treatments for AOID are effective and well tolerated in many patients, a continued demand persists for more efficacious alternatives to the limited modalities available to clinicians.

Summary

Several promising modalities for AOID, particularly for allergic conjunctivitis, immune treatments for uveitis and dry eye syndrome are in late-stage development that could offer optimal treatment paradigm once available in the clinic.

Keywords

allergies, anti-inflammatory drugs, conjunctivitis, dry eye disorders, ocular allergy, tear film dysfunction

INTRODUCTION

Eye disorders are widely prevalent, with an estimated approximately 3.5 million Americans aged at least 40 either blind or having impaired vision. Anterior ocular inflammatory disease (AOID) affects over 40% of the U.S. population. In addition to the bacterial and viral infections, these comprise ocular allergies and dry eye syndromes (DES) or tear film dysfunction that often present as comorbid conditions [1[¶],2–4].

Clinicians are becoming increasingly more aware of these conditions because of greater understanding of the underlying mechanisms; however, treatment options for AOID remain limited. In recent years, there has been significant interest in developing therapies for ocular allergies [5,6[¶]], DES [7–9], and eye infections [10], with research mostly focused on decreasing ocular surface inflammation. Investigational products, in addition to targeting the mediators liable for the clinical signs and symptoms in AOID, are also aiming to restore the homeostatic environment by addressing both the innate and adaptive immune systems [11[¶]].

OPHTHALMOLOGICAL ANTI-INFECTIVES

A wide range of pathogens are capable of attacking the surface or interior of the eye and cause a great

number of infections, with staphylococci and adenoviral conjunctivitis being the most prevalent, whereas blepharitis, hordeolum (stye), and keratitis also affect a significant number of patients.

Mostly, topical agents are indicated for the less-severe ocular surface infections with varying success [12]. Today, the most potent antibacterial agents available are the third-generation and fourth-generation quinolones; however, aminoglycoside drugs remain more cost-effective. More severe conditions could require systemic antibacterial therapy or subconjunctival injections.

Leading anti-infective brands in the market include Vigamox/Vegamox (moxifloxacin, Novartis, Basel, Switzerland), Cravit (levofloxacin, Daiichi Sankyo, Tokyo, Japan/J&J, New Jersey, USA), Zymar (gatifloxacin, Allergan, Irvine, CA, USA), and AzaSite (azithromycin 1%, Inspire, Raleigh, NC, USA, now Merck & Co., Whitehouse Station, NJ, USA).

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KEY POINTS

- Currently, there has been an expanding list of topical agents that are mostly indicated for the ocular surface inflammatory disorders (allergy, tear film abnormalities, and infections) with varying success, whereas the more severe conditions may require systemic or more localized therapy.
- Clinicians mostly prescribe topical antiallergic (antihistamines, mast cell stabilizers, or a combination of these) drugs to manage ocular allergies, with the newer agents having demonstrated more than one anti-inflammatory mechanism (dual or multiple acting agents).
- Future treatments of allergic anterior segment inflammation may include the combination of agents, as the comorbidity of conditions such as dry eye syndrome and ocular allergy are known to coexist and treatment initiatives focusing on only one condition.
- In recent years, significant advances have been made in the pharmacotherapy for anterior ocular inflammatory disease (AOID) with the recognition of conjunctival surface as an active immunological target, particularly targeting the inflammatory mediators liable for the clinical signs and symptoms in AOID; new therapies are seeking to address the innate and adaptive immune systems and restore the ocular surface environment such as a selective glucocorticoid receptor antagonist, cyclosporine for DES, purinergic receptor 2, and TNF α .

Moxifloxacin and levofloxacin are broad-spectrum fluoroquinolone antibiotics that inhibit DNA gyrase, halting cell replication. Levofloxacin is an optically active L-isomer of ofloxacin, as has been noted for other ocular pharmacological agents [13]. Gatifloxacin like moxifloxacin is a fourth-generation fluoroquinolone that is particularly effective against resistant bacteria. In 2010, U.S Food and Drug Administration (FDA) approved Zymaxid (Allergan), an increased concentration of gatifloxacin (0.5% ophthalmic solution) for bacterial conjunctivitis.

Azithromycin, a broad-spectrum macrolide indicated for bacterial conjunctivitis, has also shown improved treatment of anterior and posterior blepharitis, for which there are no FDA-approved drugs. However, recent clinical trials failed to meet the expectations [14]. Further phase II development by InSite Vision is currently underway for AzaSite Plus (ISV-502), a combination of azithromycin 1% and dexamethasone 0.1% in DuraSite (a bioadhesive ocular delivery system) for blepharitis and lid margin disease.

Other late-stage pipeline anti-infectives (Table 1) include Auriclosene (aganocide, NovaBay, Emeryville, CA, USA) for adenoviral conjunctivitis. At

present, there is no FDA-approved treatment for ocular adenoviral conjunctivitis, a highly prevalent type of 'pinkeye', with an estimated 5–10 million cases per year in the United States. As of May 2014, a phase IIb (BAYnovation) trial is ongoing for adenoviral conjunctivitis, which could be considered pivotal by the U.S. FDA.

OCULAR ANTIALLERGY

Ocular allergies affect approximately 20–40% of the U.S. general population, with seasonal allergic conjunctivitis the most prevalent [5]. Various treatment options are available to clinicians; however, topical antiallergic (antihistamines, mast cell stabilizers, or a combination of these) drugs are mostly prescribed to manage these allergies.

The leading product in this segment was Patanol/Opatanol (olopatadine, Novartis). Olopatadine is a selective histamine H₁-receptor antagonist (H1RA), indicated twice-daily for ocular itching associated with allergic conjunctivitis. Novartis's other leading antiallergy product was Pataday (olopatadine), an increased concentration (0.77%) formulation of Patanol, with the advantage of once-daily dosing. A phase III study [15] comparing Pataday with lower concentrations (0.2 and 0.1%) of olopatadine has shown a significant reduction in ocular itch.

Lastacraft (alcaftadine, Allergan) is the newest once-daily H1RA option that became available to physicians in the USA in 2011. The drug has demonstrated additional properties of a H₂ and H₄ receptor antagonist, inhibition of mast cell histamine release, decreased eosinophil chemotaxis and activation [16]. Allergan has initiated several head-to-head studies with a number of other ocular allergy agents such as olopatadine that have demonstrated equivalence [17]. Other notable antihistamine agents include Valeant's Bepreve (bepotastine besilate; Valeant, Laval, QC, Canada) with mast-cell-stabilizing activity that has also demonstrated inhibition of eosinophil migration to and activation at the inflammatory sites, with a high percentage of patients achieving 'zero' itch after installation [18].

Santen (Osaka, Japan) has launched Alesion (epinastine HCl) in Japan for allergic conjunctivitis. A H1RA with membrane-stabilizing function, the drug was first approved in 1981 for rhinitis. In May 2014, Oralair (Stallergenes, Antony, Hauts-de-Seine, France/Greer Laboratories, Lenoir, NC, USA), a sublingual allergen immunotherapy comprising five pollen extracts, was launched in the USA for grass-pollen-induced allergic rhinitis with or without conjunctivitis, of which several others have also shown effect in the treatment of allergic

Table 1. Selected late-stage pipeline for AOID

Product name	Company/sponsor	Indication	Mechanism of action	Development phase
Allergic conjunctivitis				
Vekacia (Ciclosporin)	Santen	VKC	CsA immunosuppressant	Phase III (Europe)
Prednisporin (FOV1101)	Sanofi	Allergic conjunctivitis	Fixed-combination corticosteroid	Phase IIb (USA)
Bertilimumab	iCo Therapeutics	Allergic conjunctivitis	mAb to eotaxin-1	Phase II (UK)
Anti-infective				
Auriclesone (NVC-422)	NovaBay	Anti-infective (adenoviral conjunctivitis)	Anti-infective aganocide	Phase IIb (USA/worldwide)
T-Pred	Ista	Anti-infective/ocular inflammation	Corticosteroid antibiotic aminoglycoside fixed combination	Phase III (USA)
DexaSite (ISV-305)	InSite Vision	Anti-infective/ocular inflammation/blepharitis	Corticosteroid dexamethasone/azithromycin antibiotic	Phase III (USA)
AzaSite Plus (ISV-502)	InSite Vision	Anti-infective/ocular inflammation/blepharitis	Corticosteroid/quinolone antibiotic	Phase III (USA)
BromSite (ISV-303)	InSite Vision	Pain and inflammation/postocular surgery	Analgesic NSAID	Phase III (USA)
Mapracorat	Bausch & Lomb (now Valeant)	Ocular inflammation postcataract surgery and allergic conjunctivitis	SEGRA	Phase III
Dry eye syndrome (DES)				
Restasis/Restasis X	Allergan/Merck & Co	DES, ocular surface disease	Cyclosporine/immunomodulator	Marketed USA Phase III (Europe)
Ikervis/Cyclokot (Ciclosporin)	Santen	DES	CsA immunosuppressant	Preregistration EU, Phase II (USA)
RGN 259	RegeneRx	Neurotrophic keratopathy, DES	Thymosin beta 4 peptide, angiogenesis inducer	Phase II (USA)
Diquas (diquafosol)	Santen/Allergan/Merck & Co	DES	Second-generation P2Y2 receptor agonist	Marketed (Japan, South Korea); Preregistration (China); Phase III (USA, Canada)
EGP-437	EyeGate Pharmaceuticals	DES, ocular surface disease	Corticosteroid with transscleral delivery	Phase III (USA)
DA 6034	Dong-A	DES	NF-kappa B modulator; Transcription factor regulator	Phase II (South Korea)
Immune treatments for uveitis				
Humira (adalimumab)	Abbott Laboratories	Uveitis	TNF α inhibitor	Phase III (Worldwide)
Perceiva (sirolimus)	Santen	Uveitis	Immunosuppressive, antiangiogenic, and other effects	Phase III (Worldwide)
Luveniq (voclosporin)	Lux Biosciences	Noninfectious uveitis	Calcineurin inhibitor	Phase III (North America, Europe, and Brazil)
EGP-437	EyeGate Pharmaceuticals	Uveitis	Corticosteroid with transscleral delivery	Phase III (USA)
Optiquel (B27PD)	Enzo Biochem	Uveitis	Peptide (B27PD) – a corticosteroid-sparing agent	Phase II (USA)

AOID, anterior ocular inflammatory disease; CsA, cyclosporine A; DES, dry eye syndrome; P2Y2, purinergic receptor 2; SEGRA, selective glucocorticoid receptor antagonist; TNF α , tumor necrosis factor α ; VKC, vernal keratoconjunctivitis.

conjunctivitis [19]. The product is already available in several European countries.

Key antiallergy ophthalmics in development include Santen's Vekacia, a cyclosporine A (CsA) immunomodulatory agent with the U.S. FDA

Orphan Drug Designation for vernal keratoconjunctivitis (VKC). A phase III clinical trial in VKC patients has been completed and the drug could become the first product available in Europe for such a condition. Two other promising candidates

in phase II for allergic conjunctivitis are Bertilimumab (iCo Therapeutics, Vancouver, BC, Canada) the human monoclonal antibody that binds to eotaxin-1, and prednisporin (FOV1101, Sanofi, Paris, France), a fixed-dose combination of low-dose prednisolone acetate and low-dose CsA.

ANTI-INFLAMMATION

The most frequent ocular inflammatory disorder not caused by infection is uveitis; although it is an inflammatory response of internal portion of the eye, the treatment is predominantly through topical application to the ocular surface. The autoimmune disease that causes inflammation of the uveal tract has an estimated global prevalence of 2.5 million patients. Other ocular inflammatory conditions include scleritis and chalazion, an enlarging nodule on the eyelid, formed by inflammation of the meibomian glands.

Topical corticosteroids are most widely prescribed for anterior segment inflammation, often combined with anti-infectives. NSAIDs are sometimes indicated, but are less common. Leading brands sold in this segment are TobraDex (tobramycin/dexamethasone, Novartis), Bromday (bromfenac, Valeant), and Allergan's Acular (Ketorolac). The tobramycin and dexamethasone combination is widely indicated for the treatment of steroid-responsive inflammatory eye conditions, in which there is bacterial infection or a risk of bacterial infection. Bromfenac is Valeant's once-daily NSAID follow-up to the twice-daily Xibrom for postoperative inflammation and ocular pain in patients who have undergone cataract extraction. Prolensa, a new formulation of lower (0.07%) concentration Bromday, has also been marketed.

Ketorolac, another NSAID in the family of heterocyclic acetic acid derivatives, is used for seasonal allergic-conjunctivitis-associated ocular itching and inflammation following cataract surgery [20]. It acts by inhibiting cyclooxygenase-1 and 2 (COX-1/COX-2) enzymes that result in decreased production of prostaglandins and leukotrienes.

Several promising anti-inflammatory agents are in development, including four phase III products for uveitis: Humira (adalimumab, Abbott, Abbott Park, IL, USA) – the TNF α inhibitor, Perceiva (sirolimus, Santen), Luveniq (voclosporin, Lux Biosciences, Jersey City, NJ, USA), and EGP-437 (dexamethasone phosphate, EyeGate Pharmaceuticals, Waltham, MA, USA). In April 2014, Santen reported positive data for Perceiva from the first study of a global phase III program (SAKURA), evaluating the safety and efficacy in patients with noninfectious posterior segment uveitis. Optiquel (Enzo Biochem), a corticosteroid-sparing agent, is in phase II trials in USA.

Mapracorat (Valeant), a selective glucocorticoid receptor agonist (SEGRA) [21] with desirable anti-inflammatory and immunosuppressive properties of classical glucocorticoid drugs but with fewer side-effects, has shown the potential to ameliorate forms of persistent allergic conjunctivitis and DES [1[¶],2], especially after LASIK procedures [22]. Phase III evaluation of a 3% mapracorat for epidermal surface inflammation in atopic dermatitis and postcataract surgery has been completed [23].

Also, InSite Vision has two phase III candidates for blepharitis: AzaSite Plus (ISV-502), an azithromycin and dexamethasone combination in DuraSite, and DexaSite (ISV-305) which combines dexamethasone in DuraSite. InSite is also developing BromSite (ISV-303) 0.075% bromfenac in DuraSite, which showed positive phase III data for the once-daily treatment of pain and inflammation associated with ocular surgery. InSite plans to file a new drug application (NDA) with the U.S. FDA for ISV 303 in the second half of 2014.

TEAR FILM DYSFUNCTION (DRY EYE)

DES, also known as keratoconjunctivitis sicca, is a common problem especially in the elderly. Over-the-counter (OTC) artificial tear products are generally used as the first-line option, with very few drugs available particularly to treat the severe form of dry eye.

Restasis (cyclosporine, Allergan) is the leading brand in the dry eye market. The cyclosporine emulsion is the only FDA-approved product to increase tear production in patients compromised because of ocular inflammation. Allergan is developing Restasis X (cyclosporine 0.1%), a new formulation currently in phase III in Europe.

Other leading dry eye products include Allergan's Refresh brand with Celluvisc (carboxymethylcellulose sodium), a viscous artificial tear solution, and Santen's Hyalein (sodium hyaluronate), a prescription-only medication that is available in Japan and other Asian markets.

Santen also markets Diquas (diquafosol sodium, 3%), a second-generation P2Y₂ receptor agonist for dry eye that promotes secretion of mucin and water [24–27]. It is available in Japan and Korea (October 2013), with an NDA filed in China. However, diquafosol failed to reach clinical approval in the USA. Santen has also filed for approval of Ikervis (Cyclokate; CsA) in Europe for DES. A phase II trial of cyclokate has also been conducted in the United States. Santen's pipeline also includes DE-110 (phase II), a SEGRA with a different mechanism of action from Hyalein and Diquas.

EyeGate's EGP-437, a corticosteroid solution tailored for iontophoresis, has completed a phase III

study, whereas Dong-A is developing reocflavone (DA 6034; phase II), a derivative of the flavonoid eupatilin that inhibits 5-lipoxygenase and NF-kappa B.

RegeneRx's RGN 259, a formulation of thymosin β -4 peptide, is in phase II development as a therapy to aid corneal healing in conditions such as neurotrophic keratopathy and DES. In January 2014, U.S. FDA granted RGN 259 Orphan Drug designation for the treatment of neurotrophic keratopathy.

CONCLUSION

There have been significant advances in the pharmacotherapy of the AOID over the last 25 years, with recognition of the conjunctival surface as an active immunological target. This subsequently led to progressive new treatments that address inflammatory mediators and their receptors with advancements in the development of ophthalmic agents. On the horizon are new modalities and agents such as Mapracorat, a SEGRA, other immunotherapy options, and cyclosporine for DES.

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Conflicts of interest

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