Theme Article

An Overview of Topical Immunomodulators used in Ophthalmology

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Abstract

Immunomodulators (IMT) are a novel class of drug that suppress the host immune response and inhibit the inflammatory cascade. They have several advantage over steroids when used for clinical conditions requiring long-term inflammation control. In the field of ophthalmology, IMT have been put to use for various indications like uveitis, dry eye disease, allergic eye disease, ocular surface tumours and other ocular surface disorders. It is also used intra-operatively in glaucoma surgeries, pterygium excision and photo-refractive keratectomy to increase the surgical success. The topical use of these drugs is relatively safe when compared to systemic use; hence, majority of the above conditions are treated with topical IMT. Cyclosporine A, Tacrolimus, Mitomycin C, 5-Fluorouracil and Interferon-alpha are some of the commonly used topical IMT in ophthalmic practice. Topical Lifitegrast is a recently approved drug with immunomodulatory mechanism of action that is used in management of refractory dry eye disease. In this review, we aim to provide the readers an overview of the pharmacology, clinical uses and adverse effects of these commonly used topical IMT.

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Introduction

Immunomodulator drugs have been in use ever since 1959. (1) In the past six decades, various immunomodulator drugs with different mechanism of action (MOA) have been described. These drugs were initially described for systemic use predominantly to reduce the risk of graft rejection; however, with time their indications for use has increased by leaps and bounds.[1]

Ocular surface disease (Dry eye disease (DED), allergic conjunctivitis, cicatrizing conjunctivitis), scleritis and non-infectious uveitis are few of the common clinical conditions in ophthalmology that run a chronic inflammatory course.[2–6] In the past, steroids were the only available drug to control the acute inflammatory cascade in these conditions. However, their prolonged/recurrent use was fraught with risk of blinding complications like steroid induced cataract, glaucoma and increased risk of ocular infections.[7–9] The introduction of immunomodulator drugs in the field of ophthalmology led to a paradigm shift in the management of non-infectious inflammatory conditions.[2,10] They are now used as a steroid sparing agent to achieve sustained control of inflammation which is core to the management of these clinical conditions. The use of both topical and systemic formulations of immunomodulator drugs have been described for these conditions.

In this review, we aim to provide a comprehensive overview of the topical immunomodulator drugs used in the field of ophthalmology. (Table 1) The mechanism of action, pharmacokinetics, pharmacodynamics, clinical outcome and adverse effect of the commonly used topical immunomodulator drugs will be discussed in addition to their indications for use.

Classification

Based on mechanism of action, the topical immunomodulator drugs can be classified into Inhibitors of T-cell Signalling (Calcineurin inhibitor), Alkylating agent (Mitomycin C), Anti-metabolite (5-Fluorouracil) and Biologic response modifiers (Interferon-α2b, Lifitegrast, Anakinra, Isunakinra). (Refer Table 1)

Calcineurin inhibitors

3.1. Cyclosporine A

Cycosporine A (CsA) was discovered in 1970 and was initially used for management of graft rejection following organ transplant.(11) Its ophthalmic use in the form of topical CsA 0.05% emulsion (Restasis; Allergan, Inc., Irvine, CA) and CsA 0.09% (Cequa, Sun Pharma, Cranbury, NJ, USA) is US-FDA approved for management of Dry eye disease (DED). (12) CsA is produced by fungi Tolypocladium inflatum and Beauveria nevus.[11]

3.1.1. Mechanism of action

CsA acts by inhibiting the T- cell activation.[11,13] It binds with cytoplasmic protein cyclophilin A that inhibits the activity of calcineurin. This in turn blocks the de-phosphorylation of nuclear factor for T-cell activation (NF-AT) in the cytoplasm which prevents its transport to the nucleus. This inhibits increased transcription of IL-2 gene and other genes involved in activation of T-cells. [11,13]

In addition, CsA binds with the cytoplasmic protein cyclophilin D and inhibits apoptosis or programmed cell death.[11,13] The CsA-cyclophilin D complex binds with the mitochondrial permeability pore and inhibits its opening. This in turn reduces the release of mitochondrial enzymes that are responsible for apoptosis.

3.1.2. Pharmacokinetics & Pharmacodynamics

Topical CsA is available in solution, emulsion, suspension and gel formulations.[11,13] The large molecular weight and hydrophobic nature of CsA are responsible for the poor ocular penetration. Hence, oil in water emulsions (Restasis) and micelle based solutions are used to increase its bioavailability. Use of oil vehicles results in burning, itching, redness and epithelial keratitis. Glycerine, polysorbate 80

Table 1: An Overview Of Topical Immunomodulator Drugs Use In Ophthalmic Practice

S.No.	Group	Drug	Mechanism of action	Dose	Major Indications	Adverse Effect
1	Inhibitors of T-cell Signalling	Cyclosporine A	Calcineurin inhibitor	0.05%-2% BD	•DED •VKC & AKC •Phlyctenular Keratoconjunctivitis •Acute posterior blepharitis, •Cicatrizing conjunctivitis, •Others- Sjogren syndrome, Graft rejection, Ocular rosacea, GVHD, Sterile CU, Thygeson's superficial punctuate keratitis, Ligneous conjunctivitis, SLKC, HSV stromal keratitis, and Neurotrophic CU	• Burning of eyes (Most common) • Stinging • Discharge • FB sensation • Hyperaemia
		Tacrolimus/ FK-506	Calcineurin inhibitor	0.005% to 0.1% BD (0.03% is commonly used)	• VKC, AKC • Others - Refractory uveitis, Scleritis, GVHD associated DED or Cicatrizing conjunctivitis, SLKC, Sub-epithelial infiltrates in adenoviral keratoconjunctivitis	• Transient ocular irritation • corneal infection (rare)
2	Alkylating agent	Mitomycin C	Inhibits DNA synthesis during late G1 & S phase of cell cycle by • free radical release, • DNA alkylation, • cross-links between complimentary DNA strands	0.02% - 0.04% QID 1 week on 2-3 week off OR 2 week on 2 week off	• Pterygium surgery • Glaucoma surgeries (trabeculectomy and glaucoma drainage device) • Refractive surgery -PRK • DCR • OSSN	• Scleral melt • Thin walled blebs • Bleb leak • Mild keratoconjunctivitis
3	Anti-metabolite	5-Fluorouracil	Pyrimidine analogue that inhibits DNA synthesis by inhibits thymidylate synthetase enzyme (cell-cycle specific)	2.5% - 5% (5% is commonly used)	• Glaucoma surgeries (trabeculectomy, glaucoma drainage device) • Post Trabeculectomy subconjunctival injections along with needling in failing bleb • OSSN • Pterygium surgery	• Punctate keratopathy • Keratoconjunctivitis • Filamentary keratopathy • Whorl like keratopathy • Thin walled bleb • Bleb leak
4	Biologic response modifiers	Interferon-α2b	• Enhances the phagocytic and cytotoxic activity • Inhibits biosynthetic enzymes • Decreases blood vessel proliferation • Induces apoptosis • Inactivates viral RNA	1 million IU/ ml QID (stored in refrigerator at 2-8 °C)	• Ocular surface tumours- OSSN, conjunctival papilloma, primary acquired melanosis with atypia, conjunctival melanoma, Mucosa-associated lymphoid tissue lymphoma • Recalcitrant VKC • Acyclovir resistant HSV keratitis • Others - Limbal stem cell deficiency, Mooren's ulcer, prevention post-PRK corneal haze, DME, Pseudophakic CME, Uveitic ME	• Moderate follicular conjunctivitis, • Superficial punctate keratopathy • Corneal epithelial microcyst formation • Reactive lymphoid hyperplasia
		Lifitegrast	Lymphocyte function associated antigen-1 antagonist	5% BD	Refractory DED	Eye irritation (Most common) Dysgeusia Reduced visual acuity
		Anakinra	Interleukin 1 receptor antagonist	2.5% TDS	Refractory DED	
		Isunakinra	Blocks IL-1 receptor 1 (IL-1β and IL-1Ra)	5 mg/ml and 20 mg/ml TDS	Moderate and severe DED	

Footnotes
DED- Dry eye disease; VKC- Vernal Kerato-conjunctivitis; AKC – Atopic Kerato-conjunctivitis; GVHD- Graft versus host disease; CU- Corneal Ulcer; SLKC- Superior limbic keratoconjunctivitis; HSV- Herpes simplex virus; PRK- Photo-refractive keratectomy; DNA- Deoxyribonucleic acid; DCR- Dacryocystorhinostomy; OSSN- Ocular surface squamous neoplasia; RNA;- Ribonucleic acid; DME- Diabetic macular oedema; CME- Cystoid macular oedema; ME- Macular oedema.

and sodium hydroxide can be added to these emulsions to improve patient comfort. Restasis (0.05%) is a preservative free anionic oil in water nano-emulsion that contains CsA dissolved in castor oil with polysorbate 80 as emulsifying agent and Carbomer as stabilizing agent.[11,13] Topical CsA is available in varying concentrations – 0.05%, 0.1%, 0.5%, 1% and 2%. The higher concentration formulations are not commonly available in market and are often produced in hospital compounding pharmacies. The usual dosing is twice daily; however, even QID dosing has been reported in few cases.[14]

Animal studies suggest that topical application of CsA achieves sufficient concentration for immunomodulation on the conjunctiva and cornea but very low levels (<1ng/ml) in aqueous, vitreous and plasma.

3.1.3. Indication of use

The common ophthalmic uses of topical CsA include DED, vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), phlyctenular keratoconjunctivitis (PKC), acute, posterior blepharitis, and cicatrizing conjunctivitis.[11–13,15] Its use has also been reported in Sjogren syndrome, corneal graft rejection, ocular rosacea, conjunctival graft versus host disease (GVHD) sterile corneal ulcer, Thygeson's superficial punctuate keratitis, ligneous conjunctivitis, superior limbic keratoconjunctivitis (SLKC), herpes simplex stromal keratitis, and neurotrophic ulcer with variable success.[11,13]

Literature review suggests that topical CsA is effective in management of DED and also improves the goblet cell density.[12,16] However, few studies have shown variable results suggesting need for well planned, longer follow-up studies to evaluate its role in DED.

Role of topical CsA in management of VKC is well established. It is especially useful in management of moderate to severe cases of VKC as well as shield ulcers.[17] A recent metanalysis study on efficacy of medical treatment for VKC showed similar results for CsA and tacrolimus.[18] Favourable results have also been reported with combined use of topical CsA and tacrolimus in management of severe steroid intolerant VKC.[19]

3.1.4. Adverse effect

Burning of eyes is the most common adverse effect with topical CsA followed by, stinging, discharge, foreign body sensation and hyperaemia.[11,12]

3.2. Tacrolimus

Tacrolimus, also known as FK506, is a macrolide antibiotic that has immunosuppressant effect. It is produced by fermentation of the bacteria Streptomyces tsukubaensis. Tacrolimus has been in use for management of organ transplant rejection for over three decades. Its dermatological preparation is USFDA approved for management of atopic dermatitis; however, its ophthalmic use is still off-label.

3.2.1. Mechanism of action

Tacrolimus acts by inhibiting the T-cell activation. It binds with the FK-506 binding protein within the T cells and inhibits the calcineurin activity.[10,20] This inhibits the dephosphorylation of NF-AT which in turn decreases the release of inflammatory cytokines and stimulation of other inflammatory cells.

3.2.2. Pharmacokinetics & Pharmacodynamics

Topical tacrolimus is available in solution, emulsion, cream and gel formulation.[20] It has a high molecular weight and is hydrophobic in nature. Hence, it has a poor corneal penetration, limiting the use of topical tacrolimus for management of ocular surface inflammatory conditions. A nanoscale based drug delivery system such as nanoparticle have been reported to increase the drug penetration. Topical preparation with concentrations varying from 0.005% to 0.1% is in clinical use. Majority of clinical research is based on suspension/ointment formulation of tacrolimus with concentration of 0.03% and 0.1% formulation of this drug, suggesting that even low dose topical tacrolimus has good immunosuppressive effect.[20]

3.2.3. Indication of use

Allergic eye diseases (VKC, AKC) are the most common clinical condition for which topical Tacrolimus has been used.[10,21] Other indications include refractory uveitis, scleritis, GVHD associated dry eye or cicatrizing conjunctivitis, SLKC, sub-epithelial infiltrates in adenoviral keratoconjunctivitis and post-keratoplasty to reduce risk of graft rejection.[20]

Topical tacrolimus (0.1% and 0.03%) has been reported to be effective in management of both severe and refractory allergic conjunctivitis not responding to steroids and CsA.[22] It has shown to improve both the patients' symptoms as well as clinical signs. The ability of tacrolimus to decrease giant papillae gives it an edge over CsA when dealing with such cases.[23] Few studies suggest that topical tacrolimus is more effective and more tolerable when compared to topical CsA.[24,25]

3.2.4. Adverse effect

Topical tacrolimus is usually a well-tolerated drug and has a good safety profile.[24] Transient ocular irritation upon instillation of the drug and burning sensation are the common adverse effects noted.[20] However, they do not necessitate discontinuation of this drug. Risk of corneal infection with prolonged use of topical preparation of tacrolimus is rare but has been reported in literature.[21] There is a theoretical risk of T-cell lymphoma with use of topical calcineurin inhibitors and hence a "black box" warning has been issued by USFDA against this drug.[26]

Anti-metabolite agents

4.1. Mitomycin C

Mitomycin C (MMC) is an antibiotic isolated from the bacteria Streptomyces caespitosus.[27] It was primarily used as a chemo-therapeutic agent. It is used In the field of ophthalmology, it was first used in 1963 for management of pterygium cases.[27] Ever since, the wound healing modulation properties of MMC has been put to use in various other clinical conditions in ophthalmology.

4.1.1. Mechanism of action

MMC is an alkylating agent and works primarily by inhibiting DNA synthesis during the late G1 and S phase of cell cycle.[27] However, MMC is not cell cycle specific. It inhibits DNA synthesis by various mechanisms like free radical release, DNA alkylation and, cross-links between the complimentary DNA strands. It also inhibits the RNA and protein synthesis.[27,28] It acts on both proliferating and non-proliferating cells by inducing apoptosis. It also inhibits the migration of fibroblasts.[27,28]

4.1.2. Pharmacokinetics & Pharmacodynamics

MMC is available as a lyophilised powder for intravenous preparation and liquid form (Jelmyto) for pyelocaliceal use in urothelial cancer. Its ophthalmic use is off-label. MMC is soluble in water; hence topical MMC is prepared by reconstituting the drug with distilled sterile water or balanced salt solution (BSS) in the concentration of 0.02% - 0.04%.[27,28]

4.1.3. Indication of use

Topical MMC acts by modifying the wound healing process and reducing the risk of scarring. Hence it is used in pterygium surgery to reduce risk of recurrence after pterygium excision surgery.[27] In glaucoma surgeries (trabeculectomy and glaucoma drainage device), it is used to reduce the risk of sub-conjunctival scarring and subsequent risk of failure of surgery.[29] It is used in refractive surgery, primarily in surface ablation procedures to reduce the risk of post-operative corneal haze especially when treating high refractive errors.[28] It is also put to use in dacryocystorhinostomy (DCR) surgeries at the osteotomy site to reduce the risk of fibrosis/granulation tissue formation that is often the cause for failure of DCR.[30] MMC has been reported as an effective treatment for ocular surface squamous neoplasia (OSSN) as a primary therapy, adjuvant to surgical excision and post-operatively (in cases with positive conjunctival/ deeper margins).[31] The dosing for primary /post-operative treatment is 4 times a day for 1 week followed by 2–3 weeks off until the eye is quiet. Alternatively 7 or 14 days cycle can also be used. A total of 3–4 cycles are required for treatment. Other than its established role as an adjuvant to surgery for cases of primary acquired melanosis with atypia, it has also been tried as a primary treatment for the same.[27] Rarely, its use has been reported in VKC, strabismus surgery, orbital implant surgery, optic nerve sheath fenestration, posterior capsular opacification and proliferative vitreoretinopathy (PVR).[27,32]

4.1.4. Adverse effect

MMC has a prolonged cytotoxic effect on fibroblast and vascular endothelial cells. Although, it is important for surgical success, however can result in sight-threatening complication if not used judiciously. In glaucoma drainage surgeries, it can result in thin walled blebs that can leak and put the eye at risk of hypotony, shallow anterior chamber, hypotonic maculopathy, choroidal effusion, and endophthalmitis.[27,33] It pterygium surgery, the underlying sclera can develop scleral melt.[27,33] MMC is toxic to the corneal surface and can result in mild keratoconjunctivitis.[27,33] These complications can be avoided by using appropriate concentration of MMC for appropriate duration. Sponges soaked in MMC should be used for local application during surgery to avoid contact with the surrounding surfaces. Also, the ocular surface should thoroughly irrigated after its use to avoid toxicity.

4.2. 5-Fluorouracil

5-Fluorouracil (5-FU) is a pyrimidine analogue that acts as an anti-metabolite agent and was primarily used in treatment of gastro-intestinal, head and neck, and breast cancers.[34] It also has anti-scarring properties that has been put to use in the field of ophthalmology for various clinical conditions.

4.2.1. Mechanism of action

5-FU has various cytotoxic effects. It inhibits DNA synthesis by releasing an active metabolite, 5-fluorodeoxyuridine 5′ monophosphate (FdUMP), that inhibits thymidylate synthetase enzyme which is responsible for incorporation of thymidine in DNA.[34] This action in cell-cycle specific, affecting only those cells in the S-phase of cell-cycle. 5-FU also inhibits the RNA synthesis and promotes apoptosis of tenon's capsule fibroblast.[34] However, unlike MMC, it does not affect the vascular endothelial cells.

4.2.2. Pharmacokinetics & Pharmacodynamics

5-FU is commercially available as a solution (50 mg/ml) for parenteral use in cancer patients and cream (5%) for topical application in skin malignancies. Ophthalmic use of 5-FU is off-label. The parenteral formulation is used for topical application in a concentration of 2.5% or 5%. Studies have shown that the minimum concentration of 5-FU required to induce 50% inhibition of conjunctival fibroblasts is 0.2 microgram/ml and topical application itself is sufficient to achieve this concentration in the conjunctiva, cornea and aqueous humour. Subconjunctival injection of 5-FU has also been described.[35]

4.2.3. Indication of use

Similar to MMC, 5-FU is used intra-operatively in glaucoma surgeries (trabeculectomy and glaucoma drainage device) to increase the surgical success.(36) Its post-operative use as subconjunctival injections along with needling have also been described for managing failing blebs. Various studies have compared the outcome of intra-operative MMC and 5-FU in trabeculectomy. A systematic review of literature of the same suggests low-quality of evidence for MMC being better than 5-FU.[36]

5-FU is effective is management of OSSN both as a primary therapy as well as an adjuvant to surgical excision. 1% solution of 5-FU is used for topical application 4 times a day in a cyclical pattern for a week followed by 3 weeks off.[37] A total of 4 to 6 cycles may be needed based on the observed clinical response. Intra-operative use of 5-FU in pterygium surgery has been described with limited success as recurrences were observed in 25% cases.[34] Isolated reports of its use in PVR and DCR exists in literature.[34]

4.2.4. Adverse effect

5-FU, being cell cycle specific agent, predominantly affects

the replicating cells. Hence, the corneal epithelium is most affected with its use resulting in adverse effects like punctate keratopathy, keratoconjunctivitis, filamentary keratopathy and whorl like keratopathy.[34] Its use in glaucoma surgery is associated with risk of thin walled bleb, bleb leak, hypotony, shallow anterior chamber, hypotonic maculopathy, choroidal effusion and endophthalmitis.[34] Few studies have reported that the risk of these complications are less with 5-FU when compared to MMC.[38]

Biologic response modifier

5.1. Interferon-α2b

Interferon (IFN) is a glycoprotein that has anti-neoplastic, antiviral and immunomodulatory activity It is of three types – Type 1 (IFNα, IFNβ), Type 2 (IFNγ) and Type 3. Among the different types of IFN, IFN-α 2a and 2b has been found to be of clinical use in various ophthalmic conditions.

5.1.1. Mechanism of action

IFN works by enhancing the phagocytic and cytotoxic activity, inhibiting the biosynthetic enzymes, decreasing blood vessel proliferation, inducing apoptosis and inactivating viral RNA.[39] All of the above are responsible for its immunomodulatory and anti-neoplastic effect.

5.1.2. Pharmacokinetics & Pharmacodynamics

IFN-α 2b is available as a solution for injectable use. It is prepared for topical use by adding distilled water to it to achieve a concentration of 1 million IU/ml.[37] The drug needs to be stored in refrigerator at 2-8 °C and is applied 4 times/ day. Subconjunctival injection of IFN-α 2b (3 million IU/ml) has also been described in literature.[37]

5.1.3. Indication of use

Topical IFN-α 2b is used in various ocular surface disorders including conjunctival papilloma, OSSN, primary acquired melanosis with atypia, conjunctival melanoma, Mucosa-associated lymphoid tissue (MALT) lymphoma.[31,37] It can be used as a primary therapy or adjunct to surgical excision. Both topical application (1-3 million IU/ml 4 times/ day for nearly 12 weeks or 2 month after clinical resolution) and localized sub-conjunctival injection (3 million IU/ml 0.5 ml once a week till clinical resolution) have been reported to be effective in management of OSSN.[37] Comparative studies for estimating effective topical dosage of INF-α 2b in OSSN suggests comparable result between 1million IU/ml and 3 million IU/ml.[37]

Its use has also been reported in glaucoma filtering surgeries to inhibit the tenon capsule's fibroblast proliferation. It decreases the recurrence rate following pterygium excision surgery. Topical IFN-α 2b has been reported to be useful in management of recalcitrant VKC and acyclovir resistant HSV keratitis. Few reports suggest its use in management if limbal stem cell deficiency, mooren's ulcer and prevention post-PRK corneal haze.

Its potential efficacy has been demonstrated in recalcitrant diabetic macular oedema (DME), pseudophakic cystoid macular oedema (CME) and uveitic macular oedema.[39–42] It is proposed that INF-α 2b stabilises the blood retinal barrier which helps in improvement of macular oedema.

5.1.4. Adverse effect

Topical IFN have minimal adverse effects. It can cause moderate follicular conjunctivitis,
superficial punctate keratopathy, and corneal epithelial microcyst formation.[39,40] Reactive lymphoid hyperplasia has also been reported with its use which masqueraded as orbital extension in OSSN. Subconjunctival injections are associated with flu-like symptoms.[37]

5.2. Lifitegrast

Topical Lifitegrast is the second drug after topical cyclosporine to be US-FDA approved (2016) for management of DED.[43] The OPUS trial which was a double blinded randomized controlled trial (RCT) comparing lifitegrast 5% with placebo in DED led to its FDA approval.[43,44] Lifitegrast is available as 0.2 ml single use dropper which is sufficient for both eyes.

5.2.1. Mechanism of action

Lifitegrast is a Lymphocyte function associated antigen-1 antagonist (LFA-1).[43,45] LFA-1 is an integrin present on the surface of T and B lymphocyte. Binding of lifitegrast to LFA-1 prevents interaction of lymphocyte with inter-cellular adhesion molecule 1 (ICAM-1). This in turn inhibits the adhesion, activation, migration and proliferation of inflammatory cells and release of cytokine that is responsible for the inflammatory cascade.[43,45]

5.2.2. Pharmacokinetics & Pharmacodynamics

Lifitegrast is soluble in phosphate buffered saline and can be used in concentration of upto 10% at 12 hourly interval.[43,45] However, the US-FDA approved concentration of topical lifitegrast is 5%. Studies have reported decrease in the inflammatory mediators, increase in the goblet cell density and tear production with its use.

The time to maximum concentration of lifitegrast in plasma is 5 mins suggesting a good absorption rate. The half-life in conjunctiva and sclera is 2.02 and 1.97 hrs respectively.[43,45]

5.2.3. Indication of use

Till date, DED not responding to artificial tears remains the only indication for use of topical lifitegrast.[2] Studies have shown improvement in both symptoms and signs of DED with its use over 3 months. The drug has been reported to be safe for use over 12 months; however long-term efficacy and side effects yet remains unexplored.[2]

5.2.4. Adverse effect

The most common observed adverse effects with its use include eye irritation (15%), dysgeusia (16.4%), and reduced visual acuity (11.4%).[43–45] Most of these symptoms are mild to moderate in severity. Less common adverse effects (1-5%) include blurred vision, conjunctival hyperaemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritis and sinusitis.[43]

Others

5.3.1. Anakinra

Anakinra is a recombinant Interleukin 1 receptor antagonist (IL-1Ra) that is approved for treatment of rheumatoid

arthritis.[46,47] Off-label use of topical Anakinra 2.5% has been reported in management of DED. IL-1 is intimately associated with ocular surface inflammation and is responsible for activation and migration of leucocytes which further releases inflammatory cytokines. The anti-inflammatory drugs used in DED decrease IL-1 but upregulate the IL-1 receptors. This is targeted by Anakinra to improve the DED. In an RCT comparing the effect of topical anakinra 2.5%, topical anakinra 5% and placebo applied 3 times/day for 12 weeks in cases of refractory DED, Anakinra 2.5% was found to be safe and effective in reducing symptoms and corneal epitheliopathy.[47] Studies on animal models have shown that IL-1Ra can be used to decrease infiltration of inflammatory cells in cornea, prevention of allergic eye disease, decrease corneal neovascularization, and improve the chances of graft survival in both normal-risk and high-risk corneal transplant.[48–50]

5.3.2. Isunakinra

Isunakinra (formerly called EBI-005) is a chimeric protein of IL-1β and IL-1Ra that binds and blocks IL-1 receptor 1.[51] It has the best binding characteristics of IL-1β and IL-1Ra in one molecule. It does not have agonist activity and is thermally more stable than the parent molecule. Few studies have reported the use of topical isunakinra 5 mg/ml and 20 mg/ml in management of moderate and severe DED.(51) It is applied 3 times/day for 6 weeks in these cases. Isunakinra was found to be effective and safe in management of these cases.[51]

Conclusion

Various topical immunomodulator drugs are available for ophthalmic use. A detailed knowledge of these drugs can help clinicians to shift patients requiring long-term/recurrent steroids to these drugs. Topical immunomodulators are safer when compared to steroids and protects the patient from risk of glaucoma and cataract noted with frequent use of steroids. Hence, wherever feasible, topical immunomodulator drugs should be used for long-term control of inflammation.

Literature search

A literature search was performed using PubMed Medline, the Cochrane Library Database, EMBASE, and Scopus (from 1960 onwards), with the following terms: topical immunomodulators, topical immunosuppressants, topical tacrolimus, topical cyclosporine, topical lifitegrast, topical 5-florouracil and topical mitomycin C. All relevant articles were included in this review. Priority was given to prospective studies and randomized clinical trials. However, retrospective studies and case reports were included if important. Reference lists from the selected articles were further checked to obtain further relevant articles not included in the electronic database.

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