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Editorial

Topical immunomodulators in ophthalmology

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1. Introduction

The immune system has a vital role in protecting our body from harmful substances and pathogens which could alter homeostasis and make us ill. It fights against disease causing germs, recognizes and neutralizes harmful substances and fights disease causing changes in body such as cancer cells. The innate immune system provides a preconfigured response to broad groups of stimuli whereas the adaptive immunity provides a calculated response to each stimulus by memorizing the molecules it has previously encountered. Dysfunction of the immune system can cause autoimmune diseases, inflammatory diseases and cancer.

There are many factors that act as triggers for the immunological events that lead to a diverse spectrum of ocular disorders. There are many ocular diseases which occur due to immunological causes. Ocular surface diseases, dry eye disease, allergic conjunctivitis, cicatrizing conjunctivitis, scleritis, non-infectious uveitis, graft rejection in cases of corneal transplantation, squamous neoplasia and melanoma etc are immune mediated ocular disorders that run a chronic course and may lead to visual impairment and blindness. The ocular tissues have low tolerance for inflammatory reactions. Activation of immune response finely controls the movement of specific immune cells in and out of ocular tissues. Although corticosteroids are the mainstay of treatment in several immune mediated ocular inflammatory disorders but because of associated adverse effects corticosteroid is not recommended for long term use. Immunomodulatory drugs are now used as a steroid sparing agent to achieve long-term remission of the immune mediated ocular conditions.

Immunomodulators are drugs that modify the response of immune system either by increasing (immunostimulators) or decreasing (immunosuppressives) the tissue immune response.[1] Immunostimulators are mainly used to increase the immune response against infectious diseases, tumors and in cases of primary or secondary immunodeficiency whereas immunosuppressants are used to suppress the immunity of host in cases of organ transplant and also in treatment of autoimmune diseases.[2] These drugs act at different levels of immune system and selectively inhibit or promote specific immune responsive cells. They affect the production of mediators such as cytokines.[3]

The application of immunomodulatory drugs encompasses both topical and systemic formulations.

2. Classification of Topical Immunomodulators

Based on mechanism of action, topical immunomodulators can be classified into -

1. T-cell signaling inhibitors (Calcineurin inhibitors) e.g. Cyclosporine A, Tacrolimus & Sirolimus.
2. Alkylating agent e.g. Mitomycin C
3. Anti-metabolite e.g. 5- Fluorouracil

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4. Biologic response modifiers - Interferon α2b, Lifitegrast, Anakinra & Isunakinra etc.

3. Calcineurin Inhibitors

3.1. Cyclosporin A (CsA)

CsA operates by targeting T-cell activation.[4] It accomplishes this by binding to a cytoplasmic protein called cyclophilin A, which helps in regulation of immune responses. CsA interferes with the activity of an enzyme known as calcineurin which is responsible for de-phosphorylating nuclear factor for T-cell activation (NF-AT) within the cytoplasm of T-cells.

NF-AT facilitates the transcription of genes, including the crucial IL-2 gene, necessary for T-cell activation.[5]

Furthermore, CsA also interacts with another cytoplasmic protein, cyclophilin D, which plays a important role in preventing programmed cell death or apoptosis. The CsA-cyclophilin D complex associates with the mitochondrial permeability pore, effectively preventing its opening. This action, in turn, reduces the release of mitochondrial enzymes responsible for triggering apoptosis. In summary, mechanism of action of Cyclosporine A involves inhibiting T-cell activation by disrupting key signaling pathways within the cell, as well as inhibiting programmed cell death to help maintain cell survival.

Topical cyclosporine A is available in emulsion, solution and gel formulation in different concentrations (0.05% -2%). Topical CsA is mainly used in management of meibomian gland dysfunction (MGD), dry eye disease, vernal and Atopic Keratoconjunctivitis, Phlyctenular Keratoconjunctivitis, Acute posterior blepharitis, Cicatrizing conjunctivitis, Sjogren syndrome, Graft rejection, Thygeson's superficial punctate keratitis, neurotrophic/ Mooren 's ulcer corneal ulcer, Ligneous conjunctivitis and herpes simplex keratitis etc.[6] Topical cyclosporine A can be used post postoperatively after pterygium excision, glaucoma surgery and corneal transplant. Literature review showed efficacious results of CsA in DED along with it dual role in improving goblet cell density. Its role in management of moderate to severe VKC is well-established.[7] Common adverse effects noted are burning and stinging sensation, discharge, foreign body sensation and hyperemia.

3.2. Tacrolimus

It is a macrolide antibiotic with supplementary immunosuppressive action. It is produced by fermentation of Streptomyces tsukubaensis. Tacrolimus inhibits the production of IL-2 which promotes the development and proliferation of T cells. It accomplishes this by forming a complex with the FK-506 binding protein found within T cells, which effectively hinders the activity of calcineurin.[8] This inhibition, in turn, prevents the dephosphorylation of NF-AT, leading to a reduction in the release of inflammatory cytokines and the activation of other inflammatory cells. Topical Tacrolimus is available in emulsion, solution and gel form. It has poor corneal penetration due to its high molecular weight and hydrophobic nature. Its nanoparticle formulation have been reported to increase drug penetration.

Topical Tacrolimus is primarily used in the treatment of allergic eye diseases, particularly vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC).[9] Additionally, tacrolimus is recommended in cases of refractory uveitis, scleritis, dry eye associated cicatrizing conjunctivitis, superior limbic keratoconjunctivitis (SLKC), sub-epithelial infiltrates seen in adenoviral keratoconjunctivitis, and post-keratoplasty to minimize the risk of graft rejection.[10]

Studies have reported the effectiveness of topical tacrolimus (in 0.1% and 0.03% concentrations) in managing severe and refractory allergic conjunctivitis cases that do not respond well to steroids and cyclosporine A (CsA).[11] Tacrolimus has demonstrated its capacity to alleviate both patient symptoms and clinical signs. Moreover, its ability to reduce giant papillae formation positions it as a favorable choice compared to CsA, especially in such cases.[12] Some research suggests that topical tacrolimus may offer superior efficacy and better tolerability when compared to topical CsA.[13]

Topical tacrolimus is generally well-tolerated, boasting a favorable safety profile.[14] Users may experience transient ocular irritation and a burning sensation upon instillation of the drug, but these effects are typically mild and do not necessitate discontinuation of the medication. While there is a rare risk of corneal infection associated with prolonged use of topical Tacrolimus, it has been documented in the literature.[15]

One noteworthy consideration is the theoretical risk of T-cell lymphoma associated with the use of topical calcineurin inhibitors. Consequently, the U.S. Food and Drug Administration (USFDA) has issued a "black box" warning for this drug, emphasizing the importance of closely monitoring its use in clinical practice.

4. Antimetabolite Agent

4.1. Mitomycin-C

It is an antibiotic isolated from Streptomyces caespitosus.[16] It was introduced as chemotherapeutic agent but its wound healing modulation properties holed its way into the field of ophthalmology.

Mitomycin-C (MMC) functions as an alkylating agent and exerts its primary effects by impeding DNA synthesis, particularly during the late G1 and S phases of the cell cycle.[16] Still, MMC's actions are not specific to any particular phase of the cell cycle. It disrupts DNA synthesis

through multiple mechanisms, including the release of free radicals, alkylation of DNA, and the creation of cross-links between complementary DNA strands. Furthermore, it hinders RNA and protein synthesis within cells.

It also affects non-proliferating cells by prompting apoptosis and hinders the migration of fibroblasts, which plays a pivotal role in the wound-healing process.

Topical Mitomycin-C (MMC) is primarily deployed to modify the wound healing process and reduce the risk of scarring. Its applications span a range of surgical procedures and conditions. In pterygium it is utilized to minimize the likelihood of recurrence following pterygium excision surgery. It also plays a crucial role in glaucoma surgeries such as trabeculectomy and glaucoma drainage device placement, where it mitigates the risk of subconjunctival scarring, thus reducing the potential for surgical failure.[17] MMC finds application in refractive surgery in surface ablation procedures, to lower the risk of post-operative corneal haze, especially in cases involving high refractive errors.[18]

In dacryocystorhinostomy (DCR) surgeries at the osteotomy site it is used to reduce the risk of fibrosis and granulation tissue formation, a common cause of DCR failure.[19] Additionally, MMC has been reported as an effective treatment for ocular surface squamous neoplasia (OSSN) in various capacities: as a primary therapy, as an adjuvant to surgical excision, and in post-operative care for cases with positive conjunctival or deeper margins.[20] The dosing regimen typically involves four times a day for one week, followed by 2 to 3 weeks until the eye stabilizes. Alternatively, a 7 or 14-day cycle can also be considered, typically requiring a total of 3-4 cycles for treatment.

Beyond these established uses, MMC has been explored in various other contexts, including primary acquired melanosis with atypia, and it has even been trialed as a primary treatment for certain conditions like Vernal Keratoconjunctivitis (VKC), strabismus surgery, orbital implant surgery, optic nerve sheath fenestration, posterior capsular opacification, and proliferative vitreoretinopathy (PVR).[21]

While MMC plays a critical role in ensuring surgical success, its prolonged cytotoxic effects on fibroblast and vascular endothelial cells can lead to sight-threatening complications if not used judiciously. In glaucoma drainage surgeries, MMC may result in thin-walled blebs that are prone to leakage, risking hypotony, shallow anterior chamber, hypotonic maculopathy, choroidal effusion, and endophthalmitis.[22] In pterygium surgery, it can cause scleral melt.

MMC is also known to be toxic to the corneal surface and may result in mild keratoconjunctivitis. However, these complications can be mitigated by using an appropriate concentration of MMC for the required duration. During surgery, it's advisable to use sponges soaked in MMC for localized application to avoid contact with surrounding surfaces. Post-surgery, thorough irrigation of the ocular surface is essential to minimize potential toxicity.

4.2. 5-Fluorouracil (5-FU)

5-FU is a pyrimidine analogue acting as an anti metabolite. It interferes with DNA synthesis by releasing an active metabolite known as 5-fluorodeoxyuridine 5′ monophosphate (FdUMP). FdUMP inhibits the activity of thymidylate synthetase, an enzyme responsible for incorporating thymidine into DNA.[23] This action is cell-cycle specific, affecting S-phase.

It also inhibits RNA synthesis and promotes apoptosis of fibroblasts in Tenon's capsule.

In ophthalmology, 5-FU has garnered attention for its effectiveness in addressing conditions and procedures where scar tissue formation is a concern. Some key applications include:

Glaucoma surgery, pterygium surgery, refractive surgery, and as a primary and adjuvant therapy for OSSN.

Its main adverse effect is on corneal epithelium due to its ability to disrupt replication, leading to punctate keratopathy, keratoconjunctivitis, filamentary keratopathy, and whorl-like keratopathy.

In glaucoma surgery, its usage is associated with risk of thin-walled blebs, bleb leakage, hypotony (abnormally low intraocular pressure), a shallow anterior chamber, hypotonic maculopathy, choroidal effusion, and the potential for endophthalmitis (severe eye infection).

5. Biological Response Modifier

5.1. Interferon-α2b

Interferon (IFN) is a glycoprotein with multifaceted properties like anti-neoplastic, antiviral, and immunomodulatory activities.[24] There are three main types: Type 1 (IFNα, IFNβ), Type 2 (IFNγ), and Type 3 of which IFN-α 2a and 2b have shown clinical utility in ophthalmology.

IFN boosts body's ability to engulf and eliminate foreign particles, such as pathogens or abnormal cells, by enhancing phagocytosis and cytotoxicity. It interferes with the activity of biosynthetic enzymes, disrupting the production of essential molecules necessary for cellular replication and function. It causes inhibition of blood vessels proliferation, induction of apoptosis and inactivation of viral RNA.

Topical IFN-α 2b finds application in a variety of ocular surface disorders like conjunctival papilloma, OSSN, primary acquired melanosis with atypia, lymphoma etc.[25] Its usage has been documented in glaucoma and pterygium surgeries and in refractory VKC. Also, it is useful in the treatment of refractory diabetic macular edema. Limbal stem cell deficiency, mooren's ulcer, and post-PRK corneal haze also utilise its therapeutic actions. IFN-α 2b

has demonstrated efficacy in treating recalcitrant diabetic macular edema (DME), pseudophakic cystoid macular edema (CME), and uveitic macular edema. It stabilizes the blood-retinal barrier, leading to improved macular edema.[26]

Topical IFN-α 2b typically has minimal adverse effects. Some cases of follicular conjunctivitis, superficial punctate keratopathy and corneal epithelial microcyst formation have been noted.

Various trials have garnered more interest in the usage of immunomodulators in chronic inflammatory conditions of eye which earlier relied on corticosteroid treatment alone.

One such large scale trial is FOCUS trial - Fundamentals of Care for Uveitis. It was an evidence based study that suggested usage of systemic immunomodulatory therapy in patients of Non-infectious uveitis.

There are many other immunomodulatory drugs whose systemic therapy is being utilised to treat various eye diseases.

Adalimumab, a humanized IgG1 monoclonal antibody to tumor necrosis factor was found to be efficacious in orbital myositis which was refractory to standard immunosuppressive treatment.

In the world of ophthalmology, the use of immunomodulatory drug is akin to a beacon of hope, illuminating the path toward effective management of complex eye diseases. While challenges and uncertainties exist, their potential to preserve vision and improve patients' lives is undeniable. As research continues and our understanding deepens, we can look forward to even more promising developments in this field.

5.2. Lifitegrast

It is an antagonist of lymphocyte function associated antigen -1 (LFA-1) which is an integrin present on the surface of T and B lymphocyte. It mainly acts by binding to LFA-1 and preventing the interaction of lymphocyte with intercellular adhesion molecule 1 (ICAM-1) which inhibits the adhesion, activation, migration and proliferation of leucocytes and release of inflammatory mediators which in responsible for inflammatory cascade. It is soluble in phosphate buffered saline and can be used in concentration up to 10% at 12 hourly interval. Nowadays it is indicated as topical medication only in dry eye disease not responding to artificial tears. Most common side effects of this drug are eye irritation, dysgeusia, reduced visual acuity which are mostly of mild to moderate severity.

5.3. Anakinra

It is a recombinant interleukin 1 receptor antagonist (IL-1Ra). It is used as an off label drug for the management of dry eye disease. Several studies are being performed which have shown its role in decreasing inflammatory cells in cornea, prevention of allergic eye disease, decrease corneal neovascularization and improving the chances of graft survival in patients undergoing corneal transplant.

5.4. Isunakinra

It is a chimeric protein consisting of IL-1β and IL-1Ra that binds and blocks IL-1 receptor. It is used topically in management of moderate and severe dry eye disease.

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