New and Emerging Approaches to Ocular Surface Inflammation

STEPHEN PFLUGFELDER, MD  The immune environment of the ocular surface offers multiple opportunities for pharmaceutical intervention. Following the example of other medical specialties, ophthalmologists are likely to see an influx of more targeted therapies for ocular surface inflammation.

Under normal circumstances, complex, tightly woven immune mechanisms on the ocular surface keep the eye safe from invasion or insult. A certain level of transient, physiological inflammation is a necessary part of this operation, dominated by the elements of the innate or intrinsic immune system. Inflammation becomes pathological when these same elements become dysregulated, as in autoimmune or chronic inflammatory conditions, and go from being protective to damaging of host ocular surface tissues.

Treating pathological inflammation always carries the risk of interrupting or disabling important physiological immune protections, an understanding that continues to drive antiinflammatory and immunomodulatory drug development efforts toward more specific targets. Key to success will be understanding the pathways and inflammatory mediators at play in conditions—particularly dry eye disease (DED), allergy, and, often, infection—characterized by pathological inflammation.

INTERSECTING IMMUNE PATHWAYS

In addition to the physical barriers created by the mucin glyocalyx and the tight junctions between ocular surface epithelial cells, innate ocular surface immune mechanisms include secretory proteins in tears, such as lactoferrin, lysozyme, and immunoglobulins, which exert antimicrobial and antiinflammatory effects. Transmembrane and secreted mucins are released in response to foreign, noxious, or antigenic stimuli. Secreted mucins (such as MUC5AC and MUC7) may participate in defense by preventing pathogen binding or by surrounding and removing contaminants. Resident immune cells like macrophages deal with ocular surface invasion in relatively nonspecific ways, but do have pattern-recognition receptors (including toll- and NOD-like receptors) that can respond to molecular patterns associated with pathogens or tissue damage.

Once activated, pattern recognition receptors trigger signaling pathways that lead to the production of proinflammatory cytokines, chemokines, and proteins associated with antimicrobial and tissue repair actions. Key mediators include tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-6. In

See INSIDE for: Inflammation Management and Prevention of Corneal Graft Rejection by Pedram Hamrah, MD, FACS

TARGET AUDIENCE  This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES  Upon completion of this activity, participants will be able to:
1. List three potential ocular surface antiinflammatory drug targets and weigh the advantages of available treatments to manage inflammation in ocular surface diseases.
2. Describe the immune/inflammatory pathways at work on the ocular surface.
3. Identify risk factors, mechanisms, and types of corneal graft rejection.
4. Compare strategies to manage inflammation and graft rejection.

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A CONTINUING MEDICAL EDUCATION PUBLICATION
addition to immune cells, resident ocular surface epithelial cells participate in some of these mechanisms and have their own pattern recognition receptors, including toll-like receptors (TLR) 3 and TLR4. When activated, these receptors help ramp up the immune response by releasing more proinflammatory mediators. Whether the inciting event is microbial invasion, allergen exposure, or hyperosmolar stress, eventually this cascade of inflammatory signaling can set the stage for adaptive immune mechanisms.

Adaptive immune responses are initiated when antigen presenting cells (APCs), primarily dendritic cells on the ocular surface, encounter a specific antigen. APCs activate effector T cells or prime naive T cells in the regional lymph nodes. The T cells then migrate back to the target tissue, disable and remove invading pathogens, and release cytokines that can trigger further cell recruitment and cause tissue damage. In the case of noninfectious inflammation, numerous possible autoantigens have been identified as triggers of chronic adaptive ocular surface responses. Various subsets of T helper (Th) cells may be generated depending on patterns encountered during antigen presentation. Th1 and Th17 cells are proinflammatory and implicated in the pathogenesis of DED; they secrete interferon (IFN)-gamma and IL-17, respectively. Th1 and Th2 cells are involved in the allergic immune response, secreting IL-4 and IL-5, promoting IgE synthesis, and activating eosinophils.

**DETECTING INFLAMMATION**

The inflammatory status of the ocular surface is constantly shifting, due to changes in oxygenation, tear turnover, and blink rate. At the cellular level, some degree of ocular surface inflammation is likely to be widespread. Even in the absence of frank signs of inflammation and tissue damage, we can assume that there are measurable increases in inflammatory mediators in the tears of most patients with mild to moderate DED symptoms. It is likely that a large proportion of contact lens wearers, even those who are tolerating lens wear well, have low but above-

**STATEMENT OF NEED**

The control of ocular inflammation is a critical aspect of medical and surgical ophthalmic practice. Despite their side effects, antiinflammatory drugs are used to treat a very wide range of conditions throughout the eye, from ocular surface disease and allergic conjunctivitis to posterior segment conditions. Use of antiinflammatory agents is also critical in ocular surgery, contributing greatly to patient comfort and positive outcomes. The ocular antiinflammatory landscape is changing as research reveals more about the role of inflammation in a range of ocular conditions and as new antiinflammatory agents enter the market. Twenty years ago, for example, the idea of using a topical corticosteroid to treat dry eye and/or arcus was viewed with alarm; today, it is accepted practice. Although corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstays of the ocular antiinflammatory armamentarium, a number of new agents with novel mechanisms of action (and new ocular drug delivery systems) have come to market or are being made ready for market.

As indications expand and change, and as new drugs, formulations, and delivery systems become available, clinicians require up-to-date protocols for drug selection and use. Such protocols are also needed for routine (but nevertheless off-label) uses of corticosteroids and NSAIDs because important differences in efficacy, safety, and tolerability exist among the classes and among formulations within each of these classes. By putting the latest published evidence into the context of current clinical practice, Topics in Ocular Antinflammatories equips ophthalmologists to maintain competencies and narrow gaps between their actual and optimal inflammation management practices, across the range of clinical situations in which current and novel ocular antiinflammatories may be used.

**REFERENCES**


**OFF-LABEL USE STATEMENT**

This work may discuss off-label uses of medications.

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This CME activity is sponsored by the University of Florida College of Medicine and is supported by an unrestricted educational grant from Shire. The University of Florida College of Medicine designates this activity for a maximum of 1 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. In order to receive CME credit, participants should read the report, and then take the posttest. A score of 80% is required to qualify for CME credit. Estimated time to complete the activity is 60 minutes. On completion, take the test online at [http://cme.ufl.edu/ed/self-study/toai/](http://cme.ufl.edu/ed/self-study/toai/). System requirements for this activity are: For PC users: Windows® XP, Vista, or 7, Internet Explorer® 6.0 or newer, or Mozilla® Firefox® 2.0 or newer (JavaScript™ and Java™ enabled). For Mac® users: Mac OS® X 10.4 (Tiger®) or newer, or Mozilla® Firefox® 2.0 or newer (JavaScript™ and Java™ enabled). Internet connection required: Cable modem, DSL, or better.

**DATE OF ORIGINAL RELEASE**

January 2018. Approved for a period of 12 months.

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normal ocular surface inflammation.11,12

To optimally manage inflammatory conditions of the ocular surface, there is a need for more validated biomarkers of disease and for better point-of-care tests.13 While not a direct measure of inflammation, tear osmolarity testing is a reasonable surrogate, as hyperosmolarity is recognized as a driver of inflammation, tissue damage, and symptoms in DED.13 A point-of-care test for matrix metalloproteinase-9 (MMP-9) level is useful to confirm the presence of inflammation on the surface of the eye, but not its etiology. MMP-9, an enzyme involved in tissue remodeling, is elevated in many inflammatory conditions, including DED, allergy, and very likely, infection.14

INDICATIONS FOR TREATMENT

Left untreated, mild-to-moderate ocular surface inflammation may have largely symptomatic consequences. In the cases of mild DED and allergy, at least at this point, we do not have strong evidence to suggest that tissue damage has occurred. But over time, moderate-to-severe ocular surface inflammation can induce cellular changes and even tissue remodeling. Loss of epithelial and goblet cells can lead to conjunctival scarring. Meibomian glands can become inflamed, keratinized, and atrophy, and the whole lid margin can become vascularized or irregular. Corneal neovascularization, marginal infiltrates, or recurrent erosions can lead to scarring and consequent vision changes.

There is broad consensus among eyecare practitioners that inflammation should ideally be addressed before such changes occur, but it may be difficult to determine the cutoff point in individual cases (ie, is a given patient’s chronic mild inflammation likely to progress to the point of damage?). In general, the recognition that ocular surface inflammation can be progressive has lowered many clinicians’ threshold for treatment.

CONTROLLING INFLAMMATION: CORTICOSTEROIDS

We have an increasing number of agents approved to treat ocular surface inflammation, in addition to off-label options. The most powerful and broad-acting are the topical corticosteroids. Corticosteroids exert an antiinflammatory effect primarily by binding to glucocorticoid receptors in cells. Once activated, these receptors inhibit inflammation via direct and indirect genomic effects and via non-genomic pathways (including through membrane-associated receptors).14 These numerous signaling pathways account for both the broad antiinflammatory efficacy of corticosteroids and their potential for side effects, particularly with long-term use.14,15 In the eye, these include increased intraocular pressure, cataracts, and opportunistic infections.

We are fortunate to have a range of topical ophthalmic corticosteroids available, including those that are relatively low in potency, such as fluorometholone suspension 0.1% or loteprednol etabonate suspension 0.2%.13,15 These are suitable for ocular surface inflammatory conditions, including allergic conjunctivitis, for which the 0.2% concentration of loteprednol has a specific indication.

In general, due to the potential for serious side effects, topical corticosteroids are best used in short pulses, to help control acute flare-ups of allergic conjunctivitis, DED, or blepharitis, or the sequelae of ocular surface infection (Figure 1A and B). But in certain cases, with appropriate monitoring, some of these lower-potency steroids are used longer-term to manage ocular surface inflammation. Corticosteroids with higher potency and better penetration into the anterior chamber (eg, loteprednol etabonate suspension or gel 0.5%, prednisolone acetate 1%, difluprednate emulsion 0.05%, or dexamethasone) may be reserved for postoperative and intraocular inflammation control.16

Some degree of inflammation is essential to the healing of an infectious process, but a severe inflammatory response can produce lasting damage. However, inflammation control for ocular surface infection can be tricky. The management of inflammation in cases of infectious keratitis, particularly with corticosteroids, should be undertaken cautiously, always with adequate antimicrobial coverage in place, and never in cases of active fungal, herpetic, or Acanthamoeba infection.17

The pain and inflammation of most cases of infectious conjunctivitis are managed with supportive measures, but emerging research into the use of a combination povidone iodine/dexamethasone formulation for the treatment of viral conjunctivitis is promising, showing more rapid clinical and microbial resolution versus placebo or povidone iodine alone.18

ALLERGY AND DED

Some of the newer ophthalmic anti-allergy drugs, particularly the dual-acting antihistamine/mast-cell stabilizing agents (including olopatadine solution 0.1% or 0.2%, bepotastine besilate solution 1.5%, and alcaftadine solution 0.25%), are very useful at controlling the allergic/inflammatory process on the ocular surface. These agents act at multiple points on the allergic/inflammatory cascade, blocking the H1 histamine receptor, preventing mast-cell degranulation, and inhibiting eosinophils, leukotrienes, and cytokines.9

For DED, in addition to corticosteroids, we have cyclosporine emulsion 0.05% and lifitegrast ophthalmic solution 5%. Cyclosporine inhibits the IL-2 activation of T lymphocytes, and can reduce inflammatory markers and normalize osmo-
larity in DED.\textsuperscript{19} Cyclosporine has also been shown through research and clinical experience to be useful for improving goblet cell density and reducing epithelial cell apoptosis, making it particularly appropriate for aqueous deficient and/or Sjogren disease-mediated DED.\textsuperscript{19}

Lifitegrast was FDA-approved in 2016 for DED and has also been studied in allergic conjunctivitis.\textsuperscript{20} Lifitegrast is a small-molecule integrin antagonist, believed to work by blocking the interaction between intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function-associated antigen 1 (LFA-1), which in turn inhibits T cell migration and recruitment and the release of inflammatory cytokines.\textsuperscript{8,19} Lifitegrast seems to have a more rapid onset of symptom improvement than cyclosporine, which can take months to reduce irritation symptoms; lifitegrast might be a worthwhile choice where more rapid symptom improvement is a priority.\textsuperscript{21} With cyclosporine, some clinicians advocate induction therapy with a corticosteroid such as loteprednol etabonate to hasten symptom relief.\textsuperscript{22}

Oral supplementation with essential fatty acids is often used in conjunction with other DED treatments with the aim of reducing ocular surface inflammation and improving meibum composition. Several clinical studies evaluating the use of omega-3 and/or omega-6 fatty acid supplementation have shown improvements in dry eye symptoms and measures such as tear film breakup time, osmolarity, and inflammatory markers; but more large-scale, randomized, controlled studies are needed in order to establish optimum treatment recommendations.\textsuperscript{19}

\section*{TREATMENT GAPS}

The “holy grail” of inflammation control, on the ocular surface and throughout the body, would be something with the antiinflammatory potency of a corticosteroid minus the undesirable side effects. A number of selective glucocorticoid receptor agonists and modifiers (so-called SEGRAs and SGRMs) have been under investigation in recent years. One, mapracorat, showed promising preclinical and early-stage results in a topical ophthalmic formulation and was studied for the treatment of allergic conjunctivitis, DED, and postcataract inflammation and pain; but its development has been abandoned.\textsuperscript{23} Though the possibility is no doubt exciting, the challenge of developing agents that induce some, but not all, of the effects of glucocorticoid receptor activation points to the staggering complexity of steroid signaling.\textsuperscript{14,23}

Following the example of other specialties, such as rheumatology, gastroenterology, or dermatology, it is reasonable to expect an influx of antiinflammatory therapies that target particular cytokines or inhibit a specific T-cell signaling pathway. Lifitegrast is the first FDA-approved example of an integrin antagonist in ophthalmology, but other ophthalmic drugs that work along integrin signaling pathways are being investigated. Ideally, highly targeted therapies will mean fewer unwanted adverse effects on immune function, though of course, such effects would remain a potential concern. Using the examples of cyclosporine and lifitegrast, however, we have learned that targeting T cells on the ocular surface does not seem to predispose patients to opportunistic infection.\textsuperscript{22,24}

\section*{POTENTIAL TARGETS}

An example of a targeted antiinflammatory therapy moving into ophthalmology is adalimumab, a biologic TNF-α blocker originally brought to market for the treatment of rheumatoid arthritis, which now adds uveitis to its growing list of approved indications.\textsuperscript{25} Other systemic anti-TNF-α drugs have also been tested in mouse models of DED, with mixed results, though a topically administered solution of infliximab showed increased tear volume and goblet cell density and decreased levels of inflammatory cytokines in a mouse model of DED.\textsuperscript{19}

Tofacitinib, a janus kinase (JAK) inhibitor also indicated for rheumatoid arthritis, was studied clinically in an ophthalmic formulation for DED. Though it was found to be well tolerated with efficacy comparable to cyclosporine, it did not achieve its primary efficacy endpoint and was not developed further.\textsuperscript{26,27} The continued need for reliable DED biomarkers has long challenged the design of DED treatment trials, which may have been the source of tofacitinib’s apparent failure.\textsuperscript{13,27}

A topical interleukin-1 (IL-1) receptor inhibitor (isunakinra) showed initial promise for the treatment of allergic conjunctivitis but failed to meet its primary endpoint in a phase 3 clinical trial; it has also been studied in early-phase clinical trials for DED.\textsuperscript{28,29}

IFN-γ is another important inflammatory cytokine and potential drug target for DED. Several DED therapies, including cyclosporine and lifitegrast, have been shown to block IFN-γ in vitro as a consequence of their primary actions.\textsuperscript{8,19} Antibodies against IFN-γ have shown potential in mouse models of DED and in systemic autoimmune diseases.\textsuperscript{6}

Other pipeline antiinflammatory therapies include novel delivery mechanisms or formulations that enhance ocular surface residence time or cellular penetration. A preparation of loteprednol etabonate using mucous-penetrating nanoparticles is currently being investigated in phase 3 clinical trials, for the treatment of post-cataract surgery pain and inflammation, and, separately, for the short-term treatment of DED.\textsuperscript{30}

\section*{WHERE POSSIBLE, AIM FOR EARLY, TARGETED TREATMENT}

There is a growing clinical consensus that inflammation should be addressed early, both to improve patient quality of life and to prevent the consequences of chronic inflammation. At this point in time, that probably means taking a multi-pronged approach, using one or more strategies to achieve that effect. Acute flares of ocular surface inflammation can most often be managed effectively with corticosteroids, with a number of adjunctive options that are suitable for long-term use.

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Inflammation Management and Prevention of Corneal Graft Rejection

PEDRAM HAMRAH, MD, FACS

Inflammation contributes significantly to the increased risk of corneal transplant rejection. Managing inflammation suppresses antigen delivery, angiogenesis, and lymphangiogenesis, resulting in an improved rate of long-term graft survival. Current standards for managing inflammation and graft rejection include topical and systemic corticosteroids and immunosuppressive drugs.

The cornea is an immune-privileged site, in which the inflammatory immune response to foreign antigens is generally limited. Immune privilege is mediated by multiple mechanisms: physical barriers prevent the entry and exit of cells and large molecules; immunosuppressive factors inhibit immune cell activation; and immune tolerance to antigens can arise via anterior chamber-associated immune deviation.

Inflammation, neovascularization, and previous rejection are important risk factors for corneal graft rejection. Rejection can involve any tissue layer of the graft, and more than one type can occur in the same patient. For low-risk patients, topical corticosteroids are usually sufficient to suppress inflammation and rejection. Corticosteroids can be combined with immunosuppressants in high-risk cases or where there are signs of rejection. Emerging therapies target neovascularization to combat the host immune response, and bioengineered alternatives to corneal grafts are being investigated.

RISK FACTORS

Neovascularization of the cornea significantly raises the risk of graft rejection. In particular, deep stromal vascularization of more than two quadrants in the cornea is considered to be a high-risk. Likewise, a previous graft rejection classifies a patient as high-risk. A history of graft rejection predisposes the patient to an immune response, and each subsequent graft is associated with a reduced likelihood of success. Inflammation, infection, past injuries, ocular surgery, and ocular surface diseases are also contributing factors.

Age is a risk factor because of the more vigorous immune response that occurs in younger patients. Corneal grafting in children is challenging and requires specialized surgical techniques. Rejection occurs faster and more frequently in children than in adults and is often irreversible, so postoperative management requires close monitoring and specific protocols for managing inflammation.

Size and position matter in terms of risk of graft rejection, with larger and more eccentric grafts posing a higher threat of rejection, potentially due to the closer proximity of donor antigens to the recipient’s limbal vasculature, and thus, their access to the immune system. In addition, full thickness penetrating keratoplasties have a greater risk of rejection than partial thickness transplants. The 2-year survival rate for a low-risk, full thickness penetrating keratoplasty is about 80%, whereas studies have indicated that partial corneal transplants, such as endothelial keratoplasty, have low rejections rates of 10% for DSAEK and 5% for DMEK. However, the chances of success for a patient undergoing a partial transplant are also affected by other factors, including previous episodes of rejection or ocular inflammation.

MECHANISM OF CORNEAL GRAFT REJECTION

Immune privilege may be compromised by inflammation and neovascularization. The normal cornea lacks blood and lymphatic vessels, and contains immature antigen presenting cells (APCs) in the central cornea. Inflammation or trauma can induce both angiogenesis and lymphangiogenesis, and the newly formed blood and lymphatic vessels subsequently facilitate the migration of immune cells into the cornea and the egress of APC from the cornea to draining lymph nodes.

Graft rejection is induced by activation of either host or donor APCs in the cornea, and inflammatory signals promote the migration of APCs into the corneal stroma. Donor antigens can be presented to naïve T cells directly by donor APCs, or captured and transported by host APCs to the lymph nodes.
via lymphatic vessels, where they are presented to the host immune system and presented to cytotoxic T cells and T helper cells. Sensitized T cells expand, are recruited to the eye and mount an attack on the endothelial cells or other cells in the cells. Sensitized T cells expand, are recruited to the eye and mount an attack on the endothelial cells or other cells in the cornea, resulting in tissue rejection.8,9

**RECOGNIZING GRAFT REJECTION**

Differentiating between infection and rejection can be difficult, as signs and symptoms may overlap. However, it is critically important because corticosteroids, a mainstay of graft rejection management, are contraindicated during an active infection, such as with fungal keratitis. Examination by slit-lamp biomicroscopy might not be sufficient for diagnosis, and techniques such as in vivo confocal microscopy can help to detect fungal elements or Acanthamoeba cysts and trophozoites, and thus potentially guide the correct course of treatment.16

Clinical experience shows that rejection is rarely seen within the first month in patients who have not previously undergone a corneal transplantation. However, patients with previous transplant rejections are already sensitized to donor antigens and rejection can become apparent sooner.

Typical symptoms that suggest graft rejection are redness, photosensitivity, decreasing vision, pain, and the sensation of ocular pressure. Cell and flare in the anterior chamber is also indicative of rejection. Other signs depend on the layer of tissue in which rejection is occurring.

Rejection can affect any layer of the transplanted tissue, and more than one type of rejection may occur at the same time. Corneal graft rejection can be classified into four types, based on affected layer: 

1. Epithelial rejection is characterized by a raised epithelial demarcation line, indicating damaged donor epithelial cells.
2. Subepithelial rejection is characterized by whitish subepithelial infiltrates of 0.2 mm to 0.5 mm between the epithelium and the stroma.
3. Stromal rejection features stromal edema and scarring, and occurs close to sites of neovascularization in the stroma.
4. Endothelial rejection, the most common form, is revealed by corneal edema and an endothelial rejection line, the Khodadoust line, that moves from the periphery to the center of the graft.

**MINIMIZING RISK**

Prior to performing corneal transplant surgery, it is advisable to ensure that inflammation is absent and the ocular surface is healthy.10 Corticosteroids remain the first-line therapy for managing inflammation during and after surgery.17 During surgery, intravenous corticosteroids such as methylprednisolone can be used to suppress inflammation, and pulsed IV methylprednisolone (125-500mg) and dexamethasone (100mg or 1mg per kg body weight) are both effective in treating acute rejection episodes.5,8,18

Wherever possible, lamellar or partial thickness keratoplastry is preferable to full-thickness keratoplasty, because of the decreased risk of rejection and failure.19 For a patient with anterior stromal scarring, for example, performing anterior lamellar keratoplasty preserves the patient’s own endothelium, thus removing the possibility of endothelial rejection and increasing the overall chance of graft survival.

For patients with a history of HSV infection, the use of oral antivirals such as acyclovir combined with immunosuppression with cyclosporine A brings graft survival up to a rate comparable to that of low-risk grafts.10

**MANAGING INFLAMMATION AFTER SURGERY**

After surgery, it is critical to suppress inflammation to limit the recognition of donor antigens by the host immune system. In low-risk cases, topical corticosteroids applied daily

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**TABLE I Ongoing and completed clinical trials of anti-VEGF treatments for corneal neovascularization**

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Source: www.clinicaltrials.gov


may be sufficient for prophylaxis and reversing rejection, if detected early. In higher-risk situations, more aggressive anti-inflammatory therapy is advisable. When there are signs of rejection, topical steroids can be applied every hour or two. In severe cases, or for noncompliant patients, intraocular steroid injections, such as intracameral, transscleral or sub-Tenon’s triamcinolone, can be administered.

In high-risk cases, steroids can be used postoperatively in combination with topical immunosuppressive therapies such as cyclosporine A (CsA) or tacrolimus. Although topical CsA alone is probably less effective than steroid therapy, there is evidence that a combination of steroids and CsA is superior to steroids alone in high-risk cases. In cases that do not respond to topical treatment, systemic tacrolimus or CsA can be used and may be combined with pulsed steroid injection. Where there is severe rejection, patients may remain on systemic immunosuppressive therapy for one or two years.

Chronic corticosteroid therapy comes with a risk of side effects, such as increased intraocular pressure (IOP), cataract formation, and secondary opportunistic infections. When patients experience elevated IOP as a response to prophylactic corticosteroid therapy, loteprednol etabonate, a corticosteroid with a demonstrated lower risk of IOP elevation (compared to, for example, prednisolone acetate or dexamethasone), can be used as an alternative.

**MONITORING PATIENTS ON LONG-TERM THERAPY**

Follow-up for patients on topical anti-inflammatory therapies is advised once per month to examine for signs of rejection for the first year. At all follow-up visits, it is useful to review possible symptoms of rejection in detail with patients, and instruct patients to call the clinic if they experience any such symptoms.

For patients who are on long-term systemic immunosuppression, some physicians may be sufficiently familiar with the drugs and their side effects to be comfortable monitoring these patients clinically and by serology. Alternatively, monitoring can be done in collaboration with the transplant surgeon.

**NEW AND EMERGING THERAPIES**

Drugs that target the vascular endothelial growth factor (VEGF) pathway have been shown to be effective in treating ocular diseases that involve neovascularization, including age-related macular degeneration and neovascular glaucoma. A number of clinical trials evaluating the efficacy of anti-VEGF drugs in suppressing corneal angiogenesis or lymphangiogenesis have been completed or are currently recruiting (Table 1).

Artificial corneas hold the potential to remove the risk of tissue rejection altogether. Keratoprostheses, synthetically generated corneas that are not fully bio-integrated and only provide restoration of central vision, are options for patients with end-stage corneal disease and those at very high risk of graft failure. Bioengineered, collagen-based corneal equivalents are being explored in animal models and clinical trials outside the United States (NCT02277054). However, keratoprostheses suffer from a lack of stable integration, can result in melting of the donor cornea, and can be extruded, and at present, bioengineered corneal equivalents only show potential for partial-thickness keratoplasty in which the endothelium remains intact.

Although these experimental therapies hold promise for minimizing the possibility of rejection, further research is needed before they become fully viable alternatives to tissue grafts. At present, the chances of success can be maximized by considering the patient’s history, choosing the most appropriate type of graft, and minimizing post-surgical inflammation with anti-inflammatories and immunosuppressives through vigilant monitoring for signs and symptoms of rejection.

**REFERENCES**


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**HAMRAH REFERENCES continue on page 8**
1. Which of the following is NOT a mediator and potential target for ocular surface antiinflammatory drugs?
A. IFN-γ
B. TNF-α
C. IL-1β
D. SGRM

2. Adalimumab is a TNF-α inhibitor recently approved for:
A. Moderate-to-severe DED
B. Vernal keratoconjunctivitis
C. Uveitis
D. Aqueous-deficient DED

3. In high-risk cases, or when there is severe rejection, corticosteroids can be combined with:
A. Topical immunosuppressants
B. Systemic immunosuppressants
C. A and B
D. None of the above

4. Risk factors for graft rejection include:
A. Previous graft rejection
B. Vascularized cornea
C. Ocular inflammation
D. All of the above

5. Which of the following is a validated biomarker of ocular surface inflammation?
A. Lipopolysaccharide
B. Matrix metalloproteinase-9
C. Immunoglobulin A
D. Hyperosmolarity

6. Bevacizumab, ranibizumab, and pazopanib may be beneficial in preventing rejection because they:
A. Inhibit inflammation
B. Inhibit VEGF activity and neovascularization
C. Inhibit PDGF activity and neovascularization
D. Kill cytotoxic T cells

7. Lifitegrast works by:
A. Blocking LFA-1 from binding ICAM-1
B. Inhibiting IL-17 release
C. Blocking histamine and stabilizing mast cells
D. Promoting MMP-9 production

8. Which type of rejection does a Khodadoust line characterize?
A. Epithelial
B. Subepithelial
C. Stromal
D. Endothelial

9. Which type of graft is likely to have the lowest risk of rejection?
A. Lamellar
B. Large
C. Eccentric
D. Full thickness

10. Pathological inflammation in DED is primarily mediated by:
A. Eosinophils
B. Th1 and Th17 cells
C. Mast cells
D. Basophils

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REFERENCES

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