Controlling Inflammation Associated with Viral Ocular Infection

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Ocular viral infections, including those caused by herpes simplex virus (HSV), varicella zoster virus (VZV), and adenovirus, may cause significant ocular inflammation with short- and long-term consequences for patients. Virus-induced inflammation associated with the active phase of infection may cause pain, photophobia, redness, or other uncomfortable symptoms. The second phase of inflammation/immune response after a viral infection has subsided or cleared has the potential for chronic damage, including irreversible loss of corneal clarity and visual acuity. During secondary immunopathologic processes, it is hypothesized that immune elements “mistakenly” target host cells containing residual viral antigens that either mimic or were not cleared by the first wave of host immunity, inciting tissue-specific inflammation and destruction.

HSV INFECTION AND IMMUNITY

Ocular HSV infection is a leading cause of corneal blindness in developed countries and its incidence may be increasing. Among ocular viral pathogens, HSV has been the most thoroughly studied because of its characteristic easy growth in vitro and established animal models of disease. Primary HSV infection typically occurs upon active viral replication in skin or mucosa; it often goes undetected or may manifest as a relatively mild upper respiratory tract infection. Afterward, HSV travels to the dorsal root ganglia or trigeminal ganglia of the face where it establishes latency. For most individuals, the virus remains dormant for life, but for a small subset of infected individuals, HSV reactivates one or more times as orofacial herpes (“cold sores”) or keratoconjunctivitis.

After the initial exposure to the virus, the body mounts an immune response in order to control viral replication. The immune response involves both innate and adaptive immune mechanisms. The innate immune mechanism is comprised predominantly of neutrophils, natural killer cells, and macrophages, which phagocytize and clear virus and infected cells and plasmacytoid dendritic cells. Dendritic cells produce type 1 interferons (IFN-α and IFN-β), then migrate to the lymph nodes and trigger adaptive immune mechanisms.

Adaptive immunity, comprised of CD4+ and CD8+ T cells, serves to lyse and clear virus-infected cells and establish latency. T cells also recruit a second wave of neutrophils, which release proinflammatory cytokines and contribute to downstream deleterious effects.

See INSIDE for:

Neuroinflammatory Processes in Glaucamatos Optic Neuropathy
Stephen D. Anesi, MD, FACS

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

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:
1. Differentiate virus-clearing immunity from pathologic immune processes.
2. Discuss current and pipeline agents for the treatment of viral infection-related ocular inflammatory processes.
3. Describe the mechanisms of neuroinflammation in GON.
4. Understand the role of neuroprotective medication in glaucoma treatment.

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TRIGGERS AND REACTIVATION

A subset of patients infected with HSV experiences one or more episodes of oral or ocular HSV infection. While clinical and molecular determinants of HSV reactivation remain unclear, suspected triggers include psychological stress, artificial or solar UV radiation, systemic infection, contact lens use, trauma, travel, hormonal changes associated with menstruation, and surgery (in particular surgery or procedures associated with corticosteroid use or UV radiation).5,6 Rarely, a patient with no history of ocular HSV will experience their first herpetic keratitis episode in the days following cataract surgery.

In an effort to understand why some people shed virus asymptomatically while others manifest a recurrence, basic researchers are focusing on inflammatory and regulatory functions of T cell subsets. For example, Yu and coworkers have shown that regulatory cells (Treg) function to dampen CD8+ T cell-mediated immune response and promote the establishment of latency.7 Treg cells are also thought to play a role in HSV reactivation by opposing resident CD8+ T cells in the trigeminal ganglion, which are thought to suppress viral reactivation.8 A goal is to develop a vaccine or therapy that boosts CD8+ T cell function (or inhibits Treg) to maintain latency and prevent recurrences in patients with HSV keratitis.8

VZV INFECTION AND IMMUNITY

Individuals who acquired VZV naturally from experiencing or being exposed to individuals with chicken pox in childhood may remain asymptomatic throughout life, and those who do become symptomatic usually exhibit a self-limiting illness.9,10 Infants born to women who have had chickenpox for the first time during pregnancy may develop a severe form of the disease.11,12 VZV infection acquired in childhood confers lifelong immunity to VZV infection.9,12 Individuals who acquired VZV naturally from experiencing or being exposed to individuals with chicken pox in childhood may remain asymptomatic throughout life, and those who do become symptomatic usually exhibit a self-limiting illness.9,10 Infants born to women who have had chickenpox for the first time during pregnancy may develop a severe form of the disease.11,12 VZV infection acquired in childhood confers lifelong immunity to VZV infection.9,12

COMPLICATIONS OF INFLAMMATION

It is useful to differentiate two categories or phases of inflammation caused by a broad range of viral infections: (1) inflammation in response to live virus, and (2) secondary inflammation after live virus has been cleared.

TOPICS IN OCULAR ANTIINFLAMMATORYS, ISSUE 27

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 infl ammation in a range of ocular conditions and as new antiinflammatory agents enter the market.13 Twenty years ago, for example, the idea of using a topical corticosteroid to treat dry eye and/or allergic conjunctivitis 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.1,4 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 between these classes and among formulations within each of these classes.13

By putting the latest published evidence into the context of current clinical practice, topics in Ocular Antiinflammatories 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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Inflammation-related complications vary based on the nature, location, and severity of the insult. Of chief concern is the potential to lose optical clarity of the cornea. For instance, immune-mediated stromal infiltration may lead to corneal thinning or perforation, immune rings or opacities, neovascularization, and/or lipid leakage from new vessels. Endothelial inflammation may reduce pump function, which may lead to chronic corneal edema.12,13

There is evidence to suggest that inflammation behind the cornea due to HSV, VZV, cytomegalovirus, rubella virus, and other infectious sources plays an etiologic role in Posner-Schlossman syndrome, Fuchs heterochromic iridocyclitis, and other anterior uveitis syndromes.14-16

Prompt diagnosis and appropriate management may help reduce the incidence of these sequelae. In patients with inflammatory keratoconjunctivitis of suspected viral etiology, diagnosis is generally clinical, based mostly on the patient’s history and physical examination. Complaints of glare, decreased vision, or haziness that does not improve with glasses raise suspicion of loss of corneal clarity due to an inflammatory process.17 Rapid adenovirus antigen testing is useful when epidemic keratoconjunctivitis (EKC) is suspected.18

**TREATMENT**

The goals of treating viral ocular infections are to resolve infection, minimize inflammation, prevent sequelae, and maintain vision. Antiviral and antiinflammatory therapies should be chosen based on the causative agent, extent and location of tissue involvement, infection severity, and other relevant factors. Many superficial viral infections of the eye are self-limited and require only supportive care; however, antiviral treatment becomes necessary to treat recurrent and/or inflammatory cases of ocular infection.

Oral and topical antiviral agents are the preferred methods of treatment for HSV epithelial keratitis. Oral antiviral agents are acyclovir, valaciclovir, or famciclovir, and topical antiviral agents are acyclovir, ganciclovir, or trifluridine. Oral antiviral treatment has the benefit of being relatively inexpensive, although none are US Food and Drug Administration (FDA) approved specifically for the treatment of herpetic keratitis.

For many, topical treatment with ganciclovir is preferred to trifluridine—both of which are FDA approved and indicated for the treatment of ocular herpetic infection—due to lower ocular surface toxicity and dosing frequency (5 times vs 9 times daily with trifluridine). Corticosteroids are not indicated for treatment of acute HSV epithelial infection as they may interfere with healing and prolong viral shedding.2

Antiinflammatory therapy is mainly used in the treatment of ocular HSV and VZV infection to treat inflammation-related secondary manifestations, particularly those that may smolder for weeks to months and threaten vision, such as episcleritis, trabeculitis, lipid keratopathy, symblepharon, and the like. Topical ocular formulations of corticosteroids are effective in the aftermath of HSV and adenoviral infections for inflammation focused anteriorly in the corneal epithelium. On the other hand, inflammation associated with VZV infection may involve deeper ocular tissues that are out of reach of topical therapies, so an oral formulation may be necessary. In the case of adenoviral conjunctivitis and EKC, corticosteroids may be prescribed to reduce pain and discomfort associated with membranes and pseudomembranes and reduce risk for inflammation-associated sequelae such as conjunctival scarring, dry eye, and subepithelial infiltrates.

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**CORE CONCEPTS**

- Immunopathologic processes affecting corneal stroma, endothelium, and other tissues may occur secondary to ocular viral infection.
- T cell dynamics likely play important roles in establishing latency in neurotropic viral infections.
- Corticosteroids are the mainstay of antiinflammatory treatment for secondary immune responses to viral infections. Antiinflammatory treatment use during active infection is not advised for treatment of herpes virus infections.
- Novel agents, including a combination povidone-iodine/dexamethasone topical ocular agent, are being developed for treatment of adenoviral keratoconjunctivitis.

In the former phase, the primary pathogenic mechanism is live viral replication, although inflammation and/or neurotropic damage may also play a role. Oral or topical antiviral treatment (with adjunctive antiinflammatory treatment as needed) is indicated. Epithelial herpetic keratitis is an example of a live viral stage of infection.

In the later phase, the primary pathogenic mechanism is inflammation, specifically inflammation that is directed against residual nonreplicating viral particles and host cells that harbor them. Treatment in this stage is aimed at reducing inflammation, though antiviral coverage is also typically prescribed. Stromal keratitis, endothelitis, trabeculitis, and uveitis are examples of secondary or “metaherpetic” pathoimmunologic processes.2,9-11 Inflammation associated with HZO may involve just about any ocular tissue—conjunctiva, cornea, sclera, iris, retina, or optic nerve—and may result in a range of sequelae including corneal ulceration (with characteristic pseudodendrites), uveitis, optic neuritis, or retinal necrosis.9

Immune responses, whether directed against live viral infection or after it has been cleared, can affect any layer of the cornea.2 (Figure 1) Inflammation-related complications vary based on the

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**Figure 1:** HSV marginal keratitis. (Image courtesy of Dr. Viriya.)
Efforts to control inflammation must be balanced with the risks for corticosteroid-related side effects, including increased intraocular pressure (IOP), glaucoma, cataract development, and infection; and the treatment should be tailored to the individual. As with all corticosteroid prescribing, using the least potent corticosteroid for the shortest period of time reduces corticosteroid exposure, which may spare patients undesired side effects. However, in many instances, risks associated with corticosteroid use may be less than risks associated with insufficient inflammation control, particularly among patients susceptible to corneal complications. It is also worth considering that measures for managing corticosteroid-induced side effects—e.g., topical IOP-lowering treatment, laser trabeculoplasty, cataract removal—may be less extreme than vision-restoration measures needed for corneal degradation such as corneal transplantation.17

Off-label use of steroid-sparing antiinflammatory agents, including topical cyclosporine A and lifitegrast, might be considered for patients with absolute contraindications to corticosteroids; however, these agents have not been investigated in clinical trials for the treatment of infection-related inflammation. There is some evidence that topical cyclosporine A (in concentrations ranging from 0.05% to 2%) may promote the regression of subepithelial infiltrates in patients with EKC and be a viable steroid-sparing antiinflammatory option.17,19

LOOKING AHEAD

Agents in development are intended to reduce viral load and inflammation by novel mechanisms and formulations. The broad-spectrum antiseptic agent povidone-iodine (PVP-I)—which has been used to prevent infection in medical and surgical settings for decades—is of renewed interest to researchers in the treatment of ocular viral infection. Since PVP-I is virocidal (rather than virostatic), it may be effective in shortening the course of viral ocular infection symptoms and shedding, thus limiting transmission. Although antiviral resistance is not a major problem in the treatment of ocular viral infection, it is still noteworthy that PVP-I is not thought to induce antimicrobial resistance among viruses, bacteria, or fungal pathogens.

A topical ophthalmic suspension of PVP-I 0.6%/dexamethasone 0.1% is in clinical development for the treatment of infectious, inflammatory, and immune-related sequelae of adenoviral conjunctivitis.20 In addition to controlling inflammation and preventing sequelae, the inclusion of a corticosteroid in the formulation should reduce the irritation associated with applying povidone-iodine to the eye.

A recent randomized, controlled, double-masked phase 2 trial compared PVP-I 0.6%/dexamethasone 0.1% with PVP-I 0.6% alone and vehicle control in the treatment of laboratory-confirmed acute adenoviral conjunctivitis.20 On day 6 of treatment, clinical resolution was significantly higher among patients treated with PVP-I/dexamethasone compared with no treatment, 31.3% vs. 10.9% (P=0.0158). Further, the rate of adenoviral eradication was higher among patients treated with PVP-I/dexamethasone compared with untreated patients at days 3, 6, and 12 of treatment (P<0.02 for all).20

Results of the study show that a combination formulation PVP-I/dexamethasone drop may be a useful treatment for EKC in the future, particularly for instances that warrant aggressive use of antiinflammatories (e.g., highly symptomatic patients or the presence of membranes or persistent subepithelial infiltrates).

Other agents in early stages of development as antimicrobial/antiinflammatory treatments include a novel formulation of PVP-I, a novel formulation of another antiseptic, and two naturally occurring immune-modulating compounds—OKG-0301 (Okogen) and INV-102 (Invirsa). OKG-0301 is an ophthalmic formulation of ranpirnase, an animal RNase A protein with both antiviral and antiinflammatory properties; a human form of RNase A with antiinfective activity is present in human tears.21,22 OKG-0301 has been shown to reduce viral shedding in an animal model of ocular infection; clinical trials in patients with adenoviral conjunctivitis are planned for 2019 in Australia and 2020 in the US.

The lead compound in development at Invirsa is a small molecule modulator of the innate antiviral immune response, INV-102.23 The company states that INV-102 protects against adenovirus-induced cell death in vitro and has shown efficacy in animal models of adeno-virus keratoconjunctivitis. The molecule may have broader antimicrobial activity, including against HSV and bacteria.

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REFERENCES

Neuroinflammatory Processes in Glaucomatous Optic Neuropathy

STEPHEN D. ANESI, MD, FACS

Activation of neuroinflammatory processes, either via elevated intraocular pressure (IOP) or by IOP-independent causes, contributes to the loss of retinal ganglion cells, which is the hallmark of glaucomatous optic neuropathy. While the primary aim of treatment is to reduce IOP, neuroprotective agents may also play a role in reducing the damage caused to the optic nerve by the inflammatory response.

Many ocular diseases previously not thought to involve inflammation are now considered to have an inflammatory component. For example, inflammation is now being studied not just in diabetic macular edema, where it has long been recognized, but also in macular degeneration, cataract formation, and glaucoma. Glaucomatous optic neuropathy (GON) is a chronic, progressive, blinding disorder characterized by distinct morphologic changes of the optic nerve and retinal nerve fiber layer as well as associated changes of the visual field. Recently, the specific loss of retinal ganglion cells (RGCs) has been recognized as a feature of GON and represents the culmination of a complex neuroinflammatory process with many potential triggers ultimately affecting the optic nerve.1

IOP-DEPENDENT NEUROINFLAMMATION

The elevation of intraocular pressure (IOP) is a major driving force of neuroinflammation in the development of glaucoma. It can trigger multiple interrelated processes that initiate predominantly in the lamina cribrosa (LC), a collagenous mesh forming the barrier between intraocular and orbital subarachnoid spaces through which the RGC axons pass. A transmigratory pressure gradient can form from increased pressure in the vitreous cavity or a decrease in cerebral spinal fluid (CSF) pressure posterior to the LC.2,3 The optic nerve is sensitive to changes in this gradient, and the LC is thought to be the site of primary axonal damage.1 Proteins released from damaged RGC axons may activate immune cells at the optic nerve head (ONH).4 Elevated IOP also promotes the production of extracellular matrix (ECM) at the LC and peripapillary scleral tissue, increasing the stiffness of these structures and thereby affecting the biomechanics of the ONH.5 The two opposing viewpoints on the consequences of scleral stiffening are either that it protects the ONH from the effects of pressure or it may endanger the ONH via a reduced ability to absorb pressure in areas external to the LC. Scleral stiffening also occurs with age, which is a risk factor for glaucoma.

IMMUNE ACTIVATION

The resident immune cells of the central nervous system (CNS), called glial cells, are thought to play a central role in neuroinflammation in glaucoma. The major types of glial cells are microglia and astrocytes, both of which are present at the retina and the ONH. Under normal physiological conditions, glial cells are heavily involved in maintaining the health of nerve tissue.3 Under sustained inflammatory stimulation, dysregulated immune function can lead to neurodegenerative damage, although there is debate over whether the immune response in glaucoma is protective or pathological.6 Microglial cells are the macrophages of the CNS, while astrocytes provide support to unmyelinated axons at the ONH.7 Glials also express major histocompatibility complex (MHC) class II molecules to function as antigen-presenting cells and stimulate the innate and adaptive immune responses. The expression of toll-like receptors suggests the ability to sense stress signals and initiate an immune response.7 Glial activation occurs in the early stages of GON, prior to any detectable structural or functional damage, and is thought to cause progression of the neuroinflammatory cascade in early GON in a number of ways.4 The initial response includes the glial cells producing inflammatory mediators such as TNF-alpha and other cytokines and chemokines, triggering immune cell proliferation and recruitment of circulating peripheral monocytes into the neural tissue.7,8 This initial response may be followed by the glial cells contributing to the remodeling of the ECM in the region of the ONH, decreasing the flow of CSF into the region via paravascular channels. Recent animal studies provide strong evidence of a lymphatic pathway showing that CSF enters the optic nerve via spaces surrounding the blood vessels; disruption of this flow may cause an imbalance between the production and clearance of neurotoxins such as amyloid peptides.6 Additionally, activated microglia have a reduced ability to protect against glutamate toxicity, leading to the loss of RGCs.1 Mouse models show infiltration of macrophages and monocytes is coincident with the onset of glaucoma, suggesting a potential neurodegenerative role for peripheral immune cells similar to monocyte involvement in other human neurodegenerative disease, although their role in human glaucoma is unclear.5

Astrocytes also have a role in supporting maintenance of the blood-retinal barrier (BRB), which protects the CNS from circulating infectious or inflammatory agents.1 The neuroinflammatory milieu can compromise the BRB, one effect which may be optic disc hemorrhage in normal-tension glaucoma patients.7 In addition, damaged cells within the optic nerve can release antigens that the immune system may have not previously encountered. Hence, glaucomatous optic nerve damage, combined with decreased integrity of the BRB, exposes the immune system to those antigens which can then exacerbate the inflammation, a phenomenon known as epitope spreading.9

VASCULAR DYSREGULATION

Another mechanism that may contribute to the inflammation is vascular dysregulation. The concept of a “neurovascular unit” (formed by RGCs, endothelium, and glia), which establishes the homeostatic microenvironment of the ONH, accurately depicts the interconnected nature of the targets of the neuroinflammatory process.3,4 Vascular dysregulation from irregular or fluctuating blood
flow as occurs in nocturnal hypotension, for example, is a risk factor for neuronal damage. Vascular supply of oxygen and nutrients is critical to the health of the RGCs, and impedance of blood flow caused by increased pressure at the LC can lead to deficits in oxygenation of the RGCs. Hypoxia at the ONH can lead to conditions of oxidative stress and mitochondrial dysfunction in RGC axons. This results in energy deficits and damage to cellular proteins and DNA, and, ultimately, RGC apoptosis. Oxidative stress and the products of cellular damage also trigger glial cell activation, as previously mentioned. Vascular supply for the ONH and choroid is via the short posterior ciliary arteries, which are more sensitive to alterations in ocular perfusion pressure and vascular dysregulation than the central retinal artery, and this may explain the damage more selectively occurring at the optic nerve during changes in systemic blood pressure, perfusion pressure, and vascular dysregulation.

**INFLAMMATION AND GLAUCOMA**

Secondary glaucoma is one of the complications of inflammatory conditions of the eye, such as uveitis, which can result from the obstruction of drainage structures in the anterior segment causing elevation of IOP and optic nerve damage. Examples of inflammatory conditions in which the IOP can be very high include herpetic uveitis, Fuchs heterochromic iridocyclitis and Posner-Schlossman Syndrome, or glaucomatocyclitic crisis. Paradoxically, the corticosteroids generally used to treat ocular inflammation can, themselves, lead to glaucomatous damage. This side effect arises from two possible mechanisms; firstly, steroids increase ECM deposition by cells of the trabecular meshwork increasing outflow resistance; and secondly, they may downregulate the active outflow pathways of the trabecular meshwork. Both mechanisms result in an increase in IOP. When making decisions around treatment of such cases, practitioners concerned about the risk of IOP spike from corticosteroid use should bear in mind that uveitis and ocular inflammation can also cause GON.

**DIAGNOSIS OF GON**

Currently, the gold standard for assessing glaucomatous damage is the use of dual techniques to assess both functional and structural aspects. Using automated perimetry to assess visual field changes and optical coherence tomography (OCT) to examine the structure of the optic nerve, patients are followed over time to look for changes in either of these parameters. Structural changes are often seen to precede functional deficits, and it has been shown that as much as 35 to 50% of the retinal nerve fiber layer may be lost before a visual field defect is detected. Alternatively, in some cases of GON where dysfunctional neurons are present, individuals may present with a visual field defect before optic nerve changes are observed by OCT. If there is evidence of damage but both visual field and OCT tests are normal, techniques such as pattern electroretinography can be used to detect subtle central vision changes that occur early in glaucoma. A typical finding in these patients is an increased latency of response and decreased amplitude of both pattern electroretinogram (ERG) and visual evoked potential.

**NEUROPROTECTIVE THERAPIES FOR GON**

As elevated IOP is the only, as of yet, well-accepted modifiable risk factor for glaucoma, controlling such pressure increase is pivotal, especially when it is directly involved in inducing the neuroinflammatory cascade. IOP-lowering treatments will always be central to the successful treatment of glaucoma. Decreasing IOP, in combination with antiinflammatory and neuroprotective measures where appropriate, are key to maintaining an optimal ONH environment. This is especially so for those patients in whom lowering IOP is not sufficient to prevent damage occurring to the optic nerve.

Several proposed neuroprotective agents are available and have been used by many as off-label therapy in glaucoma. Minocycline is a medication that can regulate microglial matrix metalloproteinase (MMP) activity and has been suggested to protect against neuroinflammatory changes in glaucoma. Alpha-2 adrenergic receptor agonists, such as brimonidine and clonidine, also have a potential neuroprotective function in modulating MMP activity, decreasing amyloid beta deposition and ultimately decreasing retinal ganglion cell apoptosis. Topical brimonidine is often prescribed but not clonidine as it is a potent systemic antihypertensive. Another neuroprotective agent used by many specialists off-label for GON is the oral medication memantine, a N-Methyl-D-aspartate (NMDA)-type glutamate receptor blocker that has been shown in some studies to inhibit glutamate excitotoxicity implicated in the death of RGCs. Promising neuroprotective strategies include the Rho kinase (ROCK) inhibitors, thought to exert their therapeutic effect by a dual mechanism: 1) reducing IOP by directly modulating the trabecular meshwork to increase aqueous humour outflow, and 2) inducing relaxation of the ciliary artery smooth muscle, thereby increasing blood flow to the optic nerve to promote axonal regeneration. Recently, the US FDA approved the use of netarsudil (Rhopressa), a topical ROCK inhibitor, for use in glaucoma patients. Looking further, antitumor necrosis factor-alpha (TNF-alpha) drugs may be used for neuroprotection in cases where neuroinflammatory processes are thought to be driving the glaucoma. TNF-alpha is produced by both microglia and astrocytes and is thought to be a pro-apoptotic factor for RGCs. Specific TNF-alpha blockers, many of which are approved for other indications, have been shown to protect against RGC loss in a rat glaucoma model. This last mechanism is particularly intriguing as

**CORE CONCEPTS**

- Neuroinflammatory processes at the optic nerve may be triggered prior to any functional or structural damage being detectable.
- When IOP is elevated in the setting of ocular inflammation, anti-inflammatory treatment is critical even though there is a risk of corticosteroids exacerbating the high IOP.
- Decreasing IOP, in combination with anti-inflammatory and neuroprotective measures, is key to maintaining an optimal ONH environment in the treatment of GON.
- Some of the neuroprotective medications used to treat GON include minocycline, brimonidine, and memantine, and may later include targets such as inflammatory cytokines.
anti-TNF alpha agents have also been thought to be of great value in preventing glaucomatous injury after severe ocular surface injury, as in chemical burn or in treatment of such via keratoprosthesis.20

THE FUTURE OF GON IMAGING

Several promising developments in the imaging field could enhance practitioners’ diagnostic capabilities if developed for clinical usage. One technology currently used in academic settings pairs adaptive optics with other imaging modalities such as OCT and scanning laser ophthalmoscopy. Adaptive optics allow correction of optical aberrations in real time to enable greater image resolution, even to the level of individual cells.21 Another approach, currently under investigation in phase II clinical trials, is the Detection of Apoptosing Retinal Cells (DARC) method, in which intravenous injection of fluorescently-labelled annexin proteins is used to detect apoptotic RGCs.22 In the future, deep learning algorithms for the automated interpretation of optic disc photos may become available. In a recent study, researchers used spectral domain-OCT scans of the ONH to train a deep learning algorithm to quantify, with high precision, the amount of neuroretinal damage on matched optic disc photographs.20 This could potentially obviate the need for subjective and potentially erroneous grading of optic disc photos by human graders and could lead to detection of glaucoma prior to visual field changes, particularly in patients with normal IOP.23

CONCLUSION

GON is a progressive disorder characterised by structural and functional changes to the optic nerve, loss of retinal ganglion cells, and visual impairment. Although elevated IOP is a leading risk factor for glaucoma, GON can also occur in patients with normal IOP. An expanding body of research has implicated inflammatory processes in the pathological events that culminate in RGC loss in GON. While normalizing IOP remains the primary goal of glaucoma treatment, anti-inflammatory and neuroprotective medications have shown benefit in inhibiting the neurodegenerative changes occurring in GON. A greater understanding of the complex interplay between the immune system and neurovascular environment of the optic nerve should lead to the identification of additional therapeutic targets for the treatment of GON.

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REFERENCES

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1. Which of these is considered a mechanism behind the major proposed neuroinflammatory changes in glaucoma?
   A. Oxidative stress
   B. Vascular dysregulation
   C. Glial cell activation
   D. All of the above

2. Which of the following conditions is the most likely to involve live replicating virus?
   A. Epithelial (dendritic) keratitis
   B. Symbelpharon
   C. Trabeculitis
   D. Stomal keratitis with neovascularization

3. Topical corticosteroids are LEAST likely to be effective against a secondary inflammatory process related to
   A. HSV
   B. VZV
   C. Both
   D. Neither

4. Which of the following agents might be appropriate in the treatment of active herpetic epithelial keratitis?
   A. Dexamethasone
   B. Oral acyclovir
   C. Topical Ganciclovir
   D. B or C

5. What is the mode of action of brimonidine?
   A. Glutamate receptor blocker
   B. Alpha-1 adrenergic receptor antagonist
   C. Alpha-2 adrenergic receptor agonist
   D. Anti-TNF-alpha activity

6. Topical povidone-iodine
   A. Induces viral resistance when prescribed for brief courses
   B. Is a novel antiviral for the treatment of CMV
   C. Has broad-spectrum antiseptic properties
   D. Is currently available in combination with dexamethasone

7. Which activity has not been ascribed to activated microglia?
   A. Remodelling of ECM
   B. Reduced capability to protect against excitotoxic damage
   C. Secretion of growth factors
   D. Production of inflammatory mediators

8. Which of these inflammatory conditions is not typically associated with high IOP?
   A. Diffuse lamellar keratitis
   B. Posner-Schlossman syndrome
   C. Herpetic uveitis
   D. Fuchs heterochromic iridocyclitis

9. Which of the following is NOT a goal of ocular viral infection treatment?
   A. Resolving infection
   B. Soothing patient symptoms
   C. Inducing adaptive immune response
   D. Preventing secondary immunopathology

10. Which of these measures may be pivotal in treatment of inflammatory GON?
    A. Control of inflammation
    B. Normalization of IOP
    C. Neuroprotective agents
    D. All of the above