

Managing OHT and Glaucoma in Patients With HLA-B27 Disease

A review of the complex issues and decisions on management.

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HLA-B27 disease refers to pathologies associated with one of the human leukocyte antigen (HLA) markers that are part of the body's complex self-recognition/foreign-recognition system.

HLA-B27 is a commonly cited example of HLA-associated autoimmune disease because of its strong association with numerous systemic and ocular pathologies.¹

Aside from mature red blood cells, essentially all human cells and tissues contain surface markers that enable the body to differentiate between its own cells or tissues and foreign material. Located on chromosome 6 in humans, the major histocompatibility complex contains the HLA genes that encode components of the cell surface markers. The major histocompatibility complex holds genetic information for at least three different classes of gene products. Class I gene products (HLA-A, HLA-B, and HLA-C) are on all nucleated cells. Class II molecules (HLA-D) are most notably on macrophages and dendritic cells. Both class I and class II components participate in antigen presentation to various T cells. Class III genes code for molecules related to the body's innate immune system such as the complement cascade as well as antigen processing and presentation.²

THE ROLE OF HLA-B27 IN SYSTEMIC DISEASE

Although HLA-B27 significantly increases the risk of developing spondyloarthropathy or uveitis, the majority of people with this marker do not manifest ocular or systemic inflammation. There are numerous hypotheses regarding the role of HLA genes in autoimmune disease and why people with HLA-B27 do or do not develop autoimmune disease. Molecular mimicry is one of the most well-known hypotheses. According to this theory, the body mounts an immune reaction against an invasive pathogen with

antigens that are the same as or similar to the molecules of HLA-B27. Subsequently, the first appropriate inflammatory reaction to foreign material initiates and promotes inflammation aimed at the similar self-antigens present in the HLA-B27 molecule.³ A second theory postulates that misfolding of the protein structure of the HLA-B27 molecule triggers an immune reaction.⁴ Other research indicates that the HLA-B27 gene may be proximate to another gene or genes that are actually accountable for the autoimmune pathology.⁵

Multiple systemic diseases are closely linked with HLA-B27, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease. HLA-B27-associated uveitis is classically seen in men between the ages of 20 and 40 who have a history of one of the spondyloarthropathies or inflammatory bowel disease. HLA-B27-associated uveitis may occur independently of, concomitantly with, or sequentially before or after classic HLA-B27-associated systemic diseases. In one study, about half of the patients with newly diagnosed HLA-B27-associated uveitis had an ophthalmologic consultation prompt the identification and diagnosis of systemic HLA-B27 disease.⁶

OCULAR INVOLVEMENT

The ocular manifestations of HLA-B27-associated uveitis include typical symptoms of acute unilateral non-granulomatous anterior uveitis: decreased vision, ocular pain, photophobia, ciliary flush, keratic precipitates, mild to severe anterior chamber cell and flare, and occasional anterior chamber fibrin or hypopyon. Chronic or particularly severe inflammation may result in band keratopathy, corneal decompensation, posterior or peripheral anterior synechiae, iris bombé, anterior or posterior subcapsular cataract, pars planitis, choroiditis, cystoid macular edema, or optic disc edema.^{1,6}

INFLAMMATION AND IOP

Occasionally, the IOP in uveitic patients is low due to ciliary body dysfunction and aqueous hyposecretion. Alternatively, the IOP may rise, often significantly, due to trabeculitis, restricted trabecular outflow from inflammatory cells or debris, synechial angle closure, or iris bombé. Iatrogenic ocular hypertension (OHT) may occur due to corticosteroids administered topically, as intraocular or periocular depot injections, or systemically. It is often difficult to ascertain whether OHT is due to inflammatory dysfunction of outflow or due to a corticosteroid response. The degree of inflammation and the duration and intensity of corticosteroid use may shed light on the etiology of a patient's OHT.

As with most types of uveitis, ocular inflammation in HLA-B27 uveitis should be addressed. Clinicians should attempt to eliminate or control ocular inflammation with either corticosteroids or systemic immunomodulation; most ophthalmologists will work in concert with a uveitis specialist or rheumatologist when patients require systemic immunosuppression. This therapy may be particularly useful in patients who have significant nonocular HLA-B27 disease. Systemic immunosuppression is usually avoided if no extraocular manifestations exist. Corticosteroids should be tapered to the lowest possible dose that eliminates or reduces episodes of ocular inflammation. Often, high or frequent doses of corticosteroids are required to control inflammation. Although OHT occurs more commonly with frequent or high doses of corticosteroids, even low doses of topical corticosteroids can result in persistent or significant OHT and glaucomatous optic neuropathy in some patients.

TREATING OHT

Medication

The first-line treatment for OHT in patients with HLA-B27-associated uveitis is topical IOP-lowering agents. Aqueous suppressants such as β -adrenergic blockers (eg, timolol 0.5%), carbonic anhydrase inhibitors (eg, dorzolamide 2%), or α -adrenergic agonists (eg, brimonidine 0.15%) are typically safe and effective. Topical IOP-lowering therapy should be advanced to maintain IOPs in a "safe" range, dependent on the patient's optic nerve status and risk factors for optic nerve damage. Although prostaglandin analogues (eg, latanoprost 0.005%) and cholinergics (eg, pilocarpine 1%) are typically avoided in patients with active or poorly controlled uveitis, those with well-controlled uveitis may require and/or successfully tolerate these agents. Systemic carbonic anhydrase inhibitors (eg, acetazolamide) are typically used for short-term IOP control, but some patients may tolerate and maintain IOP control with the long-term use of oral carbonic anhydrase inhibitors.

Laser Trabeculoplasty

Laser trabeculoplasty is typically avoided in patients with active or poorly controlled uveitis, but it may be used judiciously in individuals with well-controlled uveitis. This form of therapy may precipitate an initial bout of uveitis in a predisposed patient, or it may stimulate or exacerbate inflammation in a patient with known uveitis. Occasionally after laser trabeculoplasty, inflammation can cause significant complications, including severe and sustained OHT that requires incisional surgical control.

Incisional Surgery

Microinvasive glaucoma surgery (MIGS) has not been approved for HLA-B27 or other types of uveitic glaucoma. MIGS procedures such as ab interno trabeculotomy (Trabectome; NeoMedix Corporation), placement of an iStent Trabecular Micro-Bypass Stent (Glaukos Corporation), canaloplasty, and endocyclophotocoagulation (ECP) have numerous advantages over more traditional incisional surgeries. They likely will be most successful, however, in patients with well-controlled inflammation and open anterior chamber angles. (The exception is ECP, because it does not depend on normal angle anatomy.) For example, trabeculotomy with a traditional incisional technique has been shown to be effective for treating childhood uveitic glaucoma.⁷ By extension, ab interno trabeculotomy has the potential to be as or more effective than traditional trabeculotomy.

Trabeculectomy with mitomycin C can successfully treat uveitic glaucoma, particularly well-controlled disease in patients with steroid-responsive OHT.⁸ Conjunctival fibrosis and surgical failure are more likely to occur in patients with uncontrolled inflammation. A trabeculectomy may also be complicated by hypotony in a patient with a history of inflammation due to exacerbation of the uveitis and aqueous hyposecretion. Surgery with the Ex-Press Glaucoma Filtration Device (Alcon Laboratories, Inc.) may allow for more predictable fistulization and less intraocular manipulation compared with traditional trabeculectomy, but the ostomy of the shunt can be occluded by blood, fibrin, or ocular tissue such as the iris.

Tube shunts have often been used for poorly controlled inflammatory glaucoma because of their relative resistance to conjunctival fibrosis (compared with trabeculectomy).⁹ Although the intracameral tube of the Ahmed Glaucoma Device (New World Medical, Inc.) or Baerveldt glaucoma implant (Abbott Medical Optics Inc.) is typically well tolerated by a patient with uveitis, a poorly positioned tube (eg, one rubbing against the iris) may exacerbate inflammation. Additionally, the tip of the tube can be occluded by blood, fibrin, or ocular tissue such as the iris.

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inflammation may also promote bleb encapsulation and a subsequent increase in IOP. Conversely, aqueous hyposecretion or excessive aqueous outflow through valved or nonvalved tubes or large sclerostomies may cause moderate to severe postoperative hypotony.

Although the complication is often short-lived, hypotony can require high doses of topical, periocular, or systemic steroids to normalize the IOP. An intracameral injection of viscoelastic and/or ligation or explantation of the glaucoma tube is occasionally necessary to correct postoperative hypotony. Some surgeons advocate placing a smaller-plated device to reduce the risk of postoperative hypotony. Others prefer to stage the placement of the implant or to use a nonabsorbable suture to occlude and ligate the tube. This approach reduces the risk of hypotony by allowing encapsulation of the plate prior to the intraocular placement of the tube or aqueous drainage through the tube.

Cyclodestructive procedures such as ECP or transscleral cyclophotocoagulation have a higher potential for exacerbating ocular inflammation than many other IOP-lowering procedures. In some patients who are not good candidates for other incisional surgeries, ECP or transscleral cyclophotocoagulation may be a viable alternative to control IOP or to manage a blind, painful eye.

CONCLUSION

HLA-B27-related glaucoma represents a common yet challenging form of the disease. An improved understanding of the complexities of ocular inflammation, appropriate use of topical or systemic immunosuppression, and a knowledge of the wide variety of medical and surgical options available can help clinicians prevent glaucomatous damage and ocular morbidity and preserve patients' vision. ■

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