

# Controversies in the management of Irvine-Gass syndrome

by Daniel F. Kiernan, MD



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Cystoid macular edema is the No. 1 cause of vision loss after uncomplicated cataract surgery. Given the incredibly high patient and surgeon expectations, it is without surprise that unexplained vision loss after cataract surgery is a common cause for retina consultation requests from our anterior segment colleagues. Unfortunately, there is wide variability regarding how retina specialists manage patients with Irvine-Gass syndrome (IGS), and our community lacks consensus regarding treatment approach for this condition.

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Severe postoperative cystoid macular edema associated with posterior uveitis, commonly referred to as Irvine-Gass syndrome, may occur after intraocular surgery and result in visual loss. There is little consensus on the efficacy of various topical, peribulbar, retrobulbar, or intravitreal therapeutic options compared to natural history, but patients with this condition are often referred to retinal specialists for treatment consultation. Whether you practice in a multispecialty or retina-only practice, postoperative “surprises” including visual acuity that does not meet patient expectations or decreased vision several weeks or months after anterior segment surgery often result in a retinal consultation to evaluate for macular pathology. With increasing numbers of patients paying out-of-pocket expenses for premium IOLs, intraoperative aberrometry and laser-assisted cataract surgery, patient expectations are at an all-time high, and as a retinal consultant, you may influence the patient’s final satisfaction level with the referring ophthalmologist. When examination and testing reveal macular edema, the treating physician must recognize the etiology of the edema and also understand and be able to explain all possible treatment options.

In my practice, all patients referred from my anterior segment colleagues for “blurred vision” shortly after surgery require a careful history and review of preoperative exam findings. Did the patient have preoperative optical coherence tomography (OCT) testing? If, for example, there is a thick epiretinal membrane discovered after surgery, patients will often ask, “Why wasn’t this discovered before surgery?” In this case, it is important to defend your referral sources and explain that visualization of the retinal pathology was limited prior to cataract surgery. A brunescence



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cataract often prevents complete posterior segment examination or imaging, and ultrasonography cannot detect details such as edema, epiretinal membrane, or lamellar or full-thickness macular holes. So, it is important to point out to the unhappy patient that because of the cataract it was impossible to determine whether preexisting pathology was present prior to surgery. Postoperative inflammation and posterior uveitis can also lead to cystoid macular edema (CME) or Irvine-Gass syndrome (IGS), the incidence of which is nearly 100% based on angiography,<sup>1</sup> although the majority of cases are asymptomatic without active edema evident on exam or OCT.

When symptomatic IGS-associated posterior uveitis and macular edema occur, there are several treatment options that should be discussed with the patient and tailored to suit his or her level of symptomatology. Traditionally, the natural history of IGS is spontaneous resolution without any treatment, although this may take weeks or months. For many patients, especially those who live active lifestyles or have vision-dependent occupations, this is not an ideal option, and therapies directed at reducing the inflammation and edema are warranted.

### Topical therapies

Topical drug application has remained the most common method of ocular drug delivery and is useful in the treatment of many anterior segment disorders.<sup>2</sup> This mode of drug delivery is noninvasive and selectively targets the anterior chamber structures; however, the cornea represents a significant barrier for efficient drug delivery. The corneal epithelium is a lipophilic tissue and contributes to a major reduction in penetration by hydrophilic drugs. Less than 5% of the total administered dose reaches aqueous humor,<sup>3</sup> and a significantly lower amount penetrates into the posterior segment.<sup>4</sup> A major fraction of drug following topical administration is lost by lacrimation, tear dilution, nasolacrimal drainage, and tear turnover, resulting in very low ocular bioavailability.<sup>5</sup> Studies have indicated that topical corticosteroids, nonsteroidal anti-inflammatory drugs, and carbonic anhydrase inhibitors

may be efficacious in reducing macular edema in a variety of settings including IGS.<sup>6,7</sup> In my practice, if this option is chosen, I prescribe generic prednisolone acetate, ketorolac, and dorzolamide hydrochloride, one drop each, three times per day for 4 to 6 weeks. Many patients prefer this to more invasive options, and in mild cases of IGS, improvement often has occurred on follow-up examination. Newer-generation NSAIDs including nepafenac (Ilevro; Alcon, Fort Worth, TX)<sup>6</sup> and corticosteroids such as difluprednate (Durezol; Alcon, Fort Worth, TX)<sup>8</sup> may have an improved ability to penetrate the posterior segment. If the patient was prescribed these agents for the recent anterior segment surgery, the leftover drops can be resumed rather than filling a new prescription. If the edema and visual loss persist after this time, patients are usually receptive to more aggressive treatment options.

### Peribulbar and retrobulbar therapies

Corticosteroids have been widely applied within the practice of ophthalmology to control intraocular inflammation, reduce macular edema, and inhibit neovascularization. Because they target mediators in both the inflammatory and angiogenic cascades, intraocular corticosteroids are effective in treating a wide range of ocular disorders, perhaps most notably, macular edema associated with retinal vein occlusions and posterior uveitis. In a comparative study, localized treatment using peri- or retrobulbar injections of triamcinolone was shown to reverse vision loss in the setting of IGS, with no significant differences in efficacy between either modality, although increased intraocular pressure occurred in both groups.<sup>9</sup> This is one modality that is less invasive than intravitreal injections but delivers a lower concentration of medication and therefore may be less efficacious in more severe cases of IGS. Additionally, there is a risk of inadvertent penetration of the globe, which can result in disastrous consequences.

### Intravitreal injections

Intravitreal injections have become the standard of care for many sight-threatening retinal diseases and are currently the most di-

rect way to deliver the highest dose of a medication into the posterior segment. Bevacizumab (Avastin; Genentech, South San Francisco, CA) is the most widely used intravitreal agent and is very effective in treating macular edema due to a variety of pathologies including neovascular age-related macular degeneration and diabetic macular edema. However, because it solely targets VEGF, it may not be as effective for inflammatory conditions such as IGS. In a trial consisting of 14 cases of post-cataract surgery IGS, although the mean retinal thickness decreased after intravitreal bevacizumab, the mean visual acuity remained unchanged. The authors concluded that although it is safe, bevacizumab did not result in improved visual function in patients with IGS.<sup>10</sup>

Studies using intravitreal triamcinolone to treat IGS have demonstrated improvement in visual acuity and OCT-measured macular thickness in patients whose IGS is refractory to other treatments. Two small prospective case series indicated that a single intravitreal injection of triamcinolone given for long-standing (7 to 18 months after cataract surgery) CME, either 4 mg or 8 mg, resulted in dramatic improvement in visual acuity, central macular thickness, and area of leakage on fluorescein angiogram within 1 month of treatment. However in both series, the CME recurred with no significant difference in visual acuity, macular thickness, or fluorescein angiogram findings at 3 months compared to baseline, despite repeated injections.<sup>11</sup>

In a retrospective study of 14 eyes of 14 patients with persistent (greater than 6 months' duration) post-cataract surgery CME unresponsive to conventional treatment, baseline visual acuity, OCT, and multifocal electroretinogram measurements were compared to those 12 months after 4 mg triamcinolone intravitreal injection. Both the mean visual acuity and central multifocal electroretinogram area were statistically improved compared to baseline at 3, 6, and 12 months, but mean macular thickness was only significantly improved through month 3. Mean IOP was not significantly different than baseline at 12 months, though one patient had begun receiving topical IOP-lowering treatment. These

results indicate that visual acuity and multifocal electroretinogram improvement may persist for a longer period of time than anatomic improvement.<sup>12</sup>

Other prospective and retrospective analyses have indicated short-term improvements of CME after intravitreal injections of triamcinolone, but studies with longer follow-up duration, a larger number of subjects, and placebo or alternative treatment-control design are indicated to accurately assess the long-term efficacy, safety, and need for re-treatment with this off-label modality.

### Intravitreal implants

Dexamethasone has the highest relative strength of any corticosteroid used in ophthalmic practice. A single dose of 0.18 mg/mL dexamethasone is equivalent to 1 mg/mL triamcinolone in terms of corticosteroid efficacy and is short-acting, with faster clearance from the vitreous.<sup>13</sup>

Ozurdex (dexamethasone intravitreal implant; Allergan, Irvine, CA), an intravitreal implant containing 700 µg of dexamethasone within a solid, rod-shaped poly-lactide-co-glycolide copolymer (Novadur) consisting of lactic acid and glycolic acid, is designed to release drug in a biphasic fashion, with higher doses for up to 6 weeks, followed by lower but therapeutic doses for up to 6 months. The U.S. Food and Drug Administration approved its use for retinal vein occlusion and, more recently, noninfectious posterior uveitis.

The phase 3 HURON study consisted of 229 patients with noninfectious intermediate or posterior uveitis who were randomized to a single treatment with a 0.7-mg dexamethasone implant (n = 77), 0.35-mg dexamethasone implant (n = 76), or sham procedure (n = 76). The main outcome measure was the proportion of eyes with a vitreous haze score of 0 at 2 months. The proportion of eyes with a vitreous haze score of 0 at week 8 was 47% with the 0.7-mg implant, 36% with the 0.35-mg implant, and 12% with the sham ( $P < .001$ ); the effect persisted through week 26. A gain of 15 or more letters from baseline best corrected visual acuity was seen in significantly more eyes in the implant groups than the sham

group at all study visits. The percentage of eyes with intraocular pressure of 25 mm Hg or more peaked at 7.1% for the 0.7-mg implant, 8.7% for the 0.35-mg implant, and 4.2% for the sham groups ( $P > .05$  at any visit). The incidence of cataract in phakic eyes was nine of 62 (15%) with the 0.7-mg implant, six of 51 (12%) with the 0.35-mg implant, and four of 55 (7%) with the sham groups ( $P > .05$ ).<sup>14</sup>

Because IGS is, by Gass' own definition, a form of noninfectious uveitis, the use of dexamethasone in this setting is on-label, reimbursable, and highly efficacious. In a small retrospective review, nine patients with refractory macular edema due to IGS who underwent a single intravitreal injection of dexamethasone implant experienced improvement in both macular edema and visual acuity from baseline by 1 month after treatment, and the improvement remained statistically significant throughout the 6-month study. Mean baseline vision was approximately 20/80 and improved to 20/40 ( $P = .001$ ) after month 3. The mean change from baseline macular thickness was 223.00  $\mu\text{m}$  (a 41% decrease) at month 3.<sup>15</sup> In my own practice, I have reported rapid and dramatic improvements in patients with severe IGS treated with dexamethasone.<sup>16</sup>

### Conclusion

A variety of options can be tailored to suit the needs of individual patients who present with IGS. Observation or topical therapies are more conservative approaches that may be ideally suited for mild cases, but more symptomatic degrees of posterior uveitis and macular edema may indicate that a more aggressive approach is appropriate. Bevacizumab does not seem to have a significant benefit for treating IGS. Although promising in many aspects, intraocular corticosteroids are associated with numerous vision-threatening side effects that the treating physician must take into account when determining whether treatment is appropriate. IOP elevation and cataract progression are the most commonly reported adverse effects of corticosteroid treatment. The incidence of cataract progression necessitating surgery is 8.3% to 54% in eyes receiving one or more intravitreal corticosteroid injections.<sup>17</sup>

Sterile endophthalmitis is also an uncommon complication of intravitreal injection of corticosteroids, with a reported incidence of up to 5.5%. Notably, the use of preservative-free formulations may decrease this rate.<sup>18</sup> Other complications related to intravitreal injection, including vitreous hemorrhage or lens penetration, might be avoided through judicious adherence to a predetermined intravitreal injection protocol. Novel delivery approaches using sustained-release intravitreal implants have provided benefit for patients with IGS resistant to more conservative therapy, although long-term data on ocular tissue response to continuous corticosteroid exposure are still lacking.

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