
CME ACTIVITY

Intravitreal Steroids: Balancing Effective Use With Intraocular Pressure Control

With articles by
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Jointly sponsored by the Dulaney Foundation, *Retina Today*, and *Glaucoma Today*.
Supported by an unrestricted educational grant from Allergan.



RETINA TODAY



STATEMENT OF NEED

Intravitreal corticosteroid therapy has a broad range of applicability for retinal and ocular pathology. Because steroids have anti-inflammatory and antiangiogenic properties, they are beneficial for treating several retinal conditions, including diabetic and vasculocclusive macular edema, exudative macular degeneration, pseudophakic cystoid macular edema, and posterior uveitis.¹ Corticosteroid therapy has been associated with some potential complications, notably corneal opacification and intraocular pressure (IOP) elevation, which may be a barrier to its acceptance as a suitable treatment modality. This may be to patients' detriment if an effective treatment strategy is underutilized, especially given that these complications can be effectively managed before visual symptoms become irreversible.

The most popular types of corticosteroids for ocular or retinal applications are triamcinolone acetonide, dexamethasone, and fluocinolone. Each has unique pharmacodynamic, pharmacokinetic, and safety profiles. Nevertheless, several large clinical trials have documented a risk for IOP elevation associated with each class of corticosteroid. Use of topical ocular hypotensive therapy during subsequent clinical care after a single or multiple intravitreal injections of triamcinolone acetonide (a surrogate marker for elevated IOP) has been documented as high as 20% to 60%.²⁻⁷ Transient and self-limiting IOP elevations have also been associated with intravitreal triamcinolone acetonide injections.⁸

Sustained-release corticosteroid intraocular implants are a relatively new addition to this category, offering the potential for durable drug delivery that is not dependent on patients' compliance and eliminating instillation-associated complications. However, the risk of an IOP spike after corticosteroid use may be both dose-dependent and associated with prolonged exposure. In one study, 24% of uveitis patients treated with the dexamethasone implant (Ozurdex, Allergan) needed topical therapy 6 months after implantation.⁹ After 3 years of follow-up of patients implanted with the fluocinolone device (Retisert, Bausch + Lomb), 70% of patients needed some form of glaucoma topical therapy.¹⁰ Topical therapy was required by 29% of patients within 1 year of implantation with the fluocinolone device (Iluvien, Alimera Sciences).¹¹ Some studies have noted the need for filtration glaucoma surgery between 5% and 27% among patients implanted with the Iluvien¹¹ and Retisert¹⁰ devices, respectively.

Given that there is still a strong rationale for corticosteroid therapy for the care of ocular and retinal pathologies, retina specialists using corticosteroids in any capacity should be aware of the risk factors for IOP elevation, as well as appropriate management strategies for patients displaying the clinical signs or symptoms associated with elevated IOP. Retina specialists also must be aware of when it may be appropriate to work closely with a colleague in the glaucoma field on the management of

a complex case. This could entail referral, either for incisional surgery or for long-term follow-up with diagnostic devices that may not be in a typical retina practice.

There may presently be a significant knowledge gap in retina specialists' understanding of the dynamics of steroid-induced IOP elevation. An understanding of the dose- and exposure-dependent relationship between corticosteroid use and IOP elevation would be beneficial for the total care of patients. Equally, knowledge of appropriate management strategies would equip ophthalmologists who regularly use corticosteroid therapy with confidence in dealing with the most common potential complication.

Left untreated, elevation of IOP has the potential to damage the optic nerve, which, in turn, may lead to irreversible loss of visual acuity. However, most cases of corticosteroid-induced IOP elevation can be effectively managed with topical therapy, similar to that used for treating glaucoma.^{3,4,9,12} In each of these studies, the initiation of antihypotensive therapy was deemed necessary for some patients, and the initiation of this strategy was effective in reducing pressures to acceptable levels.

Incisional surgery to manage IOP elevation secondary to corticosteroid use may still be required in some cases.^{3,4,9,12} Discussions of surgical intervention may engender additional fears of intra- and postoperative complications. However, new understanding of the surgical management of glaucoma may add context to the associated risk when weighing a patient's candidacy for surgery. For example, long-term follow up in the Tube Versus Trabeculectomy (TVT) Study suggests that shunts may confer a comparatively lower failure rate and a reduced rate of postoperative complications.¹³ Thus, even if IOP elevation secondary to corticosteroid use is deemed serious enough to warrant surgical intervention, there are strategies available to minimize the attendant risks.

A full knowledge of the dynamics of corticosteroid-induced complications will be beneficial for arming clinicians who use these drugs with a more complete understanding when counseling patients and for knowing when to initiate additional therapeutic options. It is hoped that providing this education would remove a potential barrier to greater acceptance of this class of drugs. Finally, in the interest of more complete care to patients, providing clinicians with insight into the management strategies for corticosteroid-induced complications might engender greater collaboration with colleagues in other subspecialties.

1. Kiernan DF, Mieler WF. The use of intraocular corticosteroids. *Expert Opin Pharmacother*. 2009;10(15):2511-2525.

2. Baath J, Ellis AL, Chrichton A, et al. Safety profile of triamcinolone acetonide. *J Ocul Pharmacol Ther*. 2007;23(3):304-310.

3. Gillies MC, Sutter FK, Simpson JM, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. *Ophthalmology*. 2006;113(9):1533-1538.

4. Gillies MC, Simpson JM, Billson FA, et al. Safety of an intravitreal injection of triamcinolone: results from a randomized clinical trial. *Arch Ophthalmol*. 2004;122(3):336-340.

5. Elman MJ, Aiello LP, Beck RW, et al. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema.

Ophthalmology. 2010;117(6):1064-1077.

6. Goff MJ, Jumper JM, Yang SS, et al. Intravitreal triamcinolone acetonide treatment of macular edema associated with central retinal vein occlusion. *Retina*. 2006;26(8):896-901.
7. Sallam A, Sheth HG, Habot-Wilner Z, Lightman S. Outcome of raised intraocular pressure in uveitic eyes with and without a corticosteroid-induced hypertensive response. *Am J Ophthalmol*. 2009;148(2):207-213.
8. Tammewar AM, Cheng L, Kayikcioglu OR, et al. Comparison of 4 mg versus 20 mg intravitreal triamcinolone acetonide injections. *Br J Ophthalmol*. 2008;92(6):810-813.
9. Haller JA, Bandello F, Belfort R Jr, et al. OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146.
10. Goldstein DA, Godfrey DG, Hall A, et al. Intraocular pressure in patients with uveitis treated with fluocinolone acetonide implants. *Arch Ophthalmol*. 2007;125(11):1478-1485.
11. Campochiaro PA, Hafiz G, Shah SM, et al. Famous Study Group. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology*. 2010;117(7):1393-1399.
12. Jonas JB, Degenring RF, Kreissig I, et al. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. *Ophthalmology*. 2005;112(4):593-598.
13. Gedde SJ, Schiffman JC, Feuer WJ, et al. The Tube Versus Trabeculectomy Study Group. Three-year follow up of the tube versus trabeculectomy study. *Am J Ophthalmol*. 2009;148(5):670-684.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists, glaucoma specialists and general ophthalmologists involved in the management of patients with retinal and glaucomatous disease.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Understand the potential for corticosteroid therapy to induce complications, including elevated IOP
- Distinguish between the different classes of corticosteroid therapy and relate the risks for complications associated with each
- Explain the early warning signs of elevated IOP
- Identify effective management strategies for patients requiring intervention

METHOD OF INSTRUCTION

Participants should read the CME activity in its entirety. After reviewing the material, please complete the self assessment test, which consists of a series of multiple choice questions. To answer these questions online and receive real-time results, please visit <http://www.dulaneyfoundation.org> and click "Online Courses." Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 AMA PRA Category 1 Credit.[™] The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dulaney Foundation, *Retina Today*, and *Glaucoma Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit.[™] Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Dr. Dugel states that he is an advisor or consultant for Abbott Laboratories, Acucela, Alcon, Alimera Sciences, Allergan, ArcticDx, Genentech, Lux Biosciences, MacuSight, NeoVista, Ophthotech, Ora, Regeneron, and ThromboGenics. He owns stock, stock options, or bonds from ArcticDx, MacuSight, NeoVista, and Ophthotech.

Dr. Han states that his institution receives research grant funding to support clinical trials from Acucela, Genentech, Regeneron, and Sakura.

Dr. Noecker states that he is a consultant for Alcon, Allergan, AqueSys, EndoOptiks, Glaukos, InnFocus, Lumenis, Ocular Therapeutics, Merck & Co., and Valeant Pharmaceuticals.

Dr. Singh states that he has served as a consultant to and/or served on the speakers board for Alcon, Genentech, Regeneron, and Thrombogenics.

Dr. Varma states that he had a financial agreement or affiliation during the past year with Allergan, AqueSys, Genentech, and Replenish.

All of those involved in the planning, editing, and peer review of this educational activity report no relevant financial relationships. ■

Considerations When Using Combination Therapy for Retinal Vein Occlusions

Multiple serial steroid implants can be a safe option for treatment.

BY PRAVIN U. DUGEL, MD

After almost a decade of experience with anti-VEGF pharmacotherapy for ophthalmic applications, clinicians can have no doubts that these agents are effective and safe treatments for a number of diseases. We can now treat conditions for which there were previously no reliably effective therapies, preserving vision and quality of life for our patients. At the same time, however, we recognize that many patients need chronic treatment with anti-VEGF medications in order to preserve these visual benefits.

Therefore, the question arises whether anti-VEGF monotherapy is sufficient in treatment of conditions such as retinal vein occlusion (RVO), or whether future paradigms will include some types of combination therapy for this and other diseases. Specifically, what role will intravitreal steroids, either as injections or as durable implants, play in the management of RVO and other pathologies?

This article presents an overview of several studies and my interpretation of what their results tell us. It touches on patterns of patient response to anti-VEGF therapy for branch and central RVO (BRVO and CRVO), the use of steroids in treatment of RVO, the differences between bolus and device delivery of steroids, and whether the risks of prolonged steroid use in the treatment of RVO are manageable.

WHAT THE BRAVO RESULTS TELL US

In the BRAVO randomized controlled trial in patients with BRVO, ranibizumab (Lucentis, Genentech) provided rapid, effective treatment of macular edema following BRVO.¹ The study design included an initial 6-month treatment period when patients received monthly 0.5 mg or 0.3 mg ranibizumab or sham injections. The primary efficacy endpoint was change in best corrected visual acuity (BCVA) letter score at month 6. This was followed by a 6-month as-needed (prn) treatment period with set criteria for reinjection or rescue laser.

In fact, despite its yearlong study design, almost 100% of the patient response in BRAVO came after the first 3 monthly injections. In the graph of BCVA response, there is an initial curve of improvement to month 3, followed by a plateau thereafter with minimal gain achieved, even in those who received monthly dosing (Figure 1). After

Treatment	Mean Number of Injections	% Injected at Month 6	% With No Injections	% With Laser Treatment
0.3 mg ranibizumab	2.8	41	21	31
0.5 mg ranibizumab	2.7	38	24	24
Sham/0.5 mg	3.6	79	13	24

Figure 1. As-needed ranibizumab injections during the prn period.

the first injection, 60% of the responses occurred; after the second injection, another 30% additional improvement to the initial 60% response was seen; and after the third injection, another 10% additional improvement to the second treatment was achieved.

The anatomic results in BRAVO tell a similar story. Optical coherence tomography (OCT) results show a decrease in central retinal thickness to month 3, followed by a plateau with essentially no change.

With minimal functional and anatomic gains after 3 injections, one might ask whether subsequent injections are worth a few more letters of improvement, or whether nonresponders to initial anti-VEGF therapy might benefit more from a multifactorial treatment, perhaps targeting a different pathway.

Of the patients in BRAVO who received prn ranibizumab 0.5 mg treatment after month 6, only 24% needed no treatment. That is, three-quarters of the patients continued to require treatment.

Key findings from BRAVO include the fact that most of the efficacy occurs after the very first injection, almost the entire efficacy occurs by month 3, and marginal improvement was seen between months 3 and 6. Also in BRAVO, 38% of patients did not achieve a BCVA better than 20/40 or a central retinal thickness of 250 μ m or less after 6 injections. In addition, 38% to 49% of patients required injections in the first month of the prn period, and only 20% of patients did not need retreatment after month 6.

My interpretation of these findings from BRAVO is

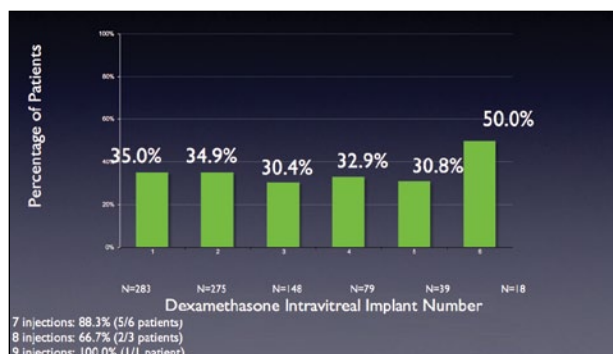


Figure 2. Percentage of patients with ≥ 3 lines improvement after each injection of the dexamethasone implant.

that there is a subset of patients with BRVO who require more than just anti-VEGF treatment. BRAVO also suggests that if we are to offer another treatment, we should start early because the patients who were crossed over from sham treatment never caught up, in visual or OCT results, with those who were treated from baseline.

RATIONALE FOR STEROID TREATMENT

In my experience, there are 3 kinds of patients with BRVO. There are those who respond to anti-VEGF therapy with resolution of macular edema. This is a minority of patients. There are those who respond but whose macular edema recurs after treatment is stopped, so that further retreatment is needed. This is the majority of patients, in my experience. There are a few patients who simply never respond to anti-VEGF therapy. In all, then, patients with BRVO are likely to respond to anti-VEGF monotherapy, but that response in most cases is not sustained, and most needed continued treatment or some other treatment option.

Given this profile, when is combination treatment with a corticosteroid called for, and what type of delivery would be preferred? The rationale for steroid use includes a well-documented inflammatory component in the pathophysiology of macular edema. The efficacious effect of dexamethasone on inflammatory mediators has been well studied.²⁻⁵

With bolus injection of steroid, such as intravitreal triamcinolone acetonide (IVTA) injection, there is a rapid increase and a rapid decrease in drug levels.^{3,4} That is not a desirable, safe pharmacokinetic profile. The dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan), by contrast, has a predictable release profile, with an increase in the early period followed by a gradual decline.⁶ It does not have what is known as zero-order kinetics, but the sustained release dosage is well characterized and predictable.

PREDICTABILITY

Knowing that a significant percentage of patients with BRVO will not respond to anti-VEGF monotherapy in a

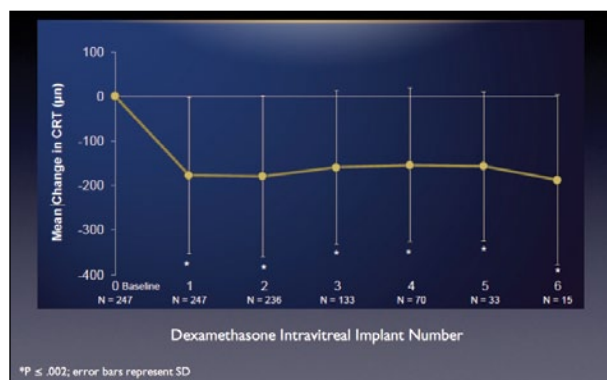


Figure 3. Change in central retinal thickness from baseline after each injection.

sustained manner, as seen in BRAVO, it would be helpful to have a way to predict early in the course of treatment which patients might benefit from combination therapy. A recent post hoc analysis⁷ of data from the BRAVO¹ and CRUISE⁸ studies offers some clues.

Bhisitkul and colleagues⁷ analyzed data from the 2 studies to determine whether time-domain OCT images from baseline or month 3 provided predictive signals regarding visual outcomes. Their analysis determined that if patients were categorized as early ranibizumab responders—that is, if they had central retinal thickness on OCT of 250 μm or less at month 3—they had excellent final visual outcomes. By contrast, if patients had not improved significantly on OCT by month 3, they were likely to require long-term treatment. At month 3, cystoid macular edema (CME) was resolved in approximately 50% in those with either BRVO or CRVO who were treated with ranibizumab. Those who had residual CME at month 3 had worse visual outcomes at month 6.

BOLUS VS IMPLANT

A study by Chee et al⁹ compared the efficacy and complications of bolus injection of IVTA with those of the dexamethasone intravitreal implant. This retrospective study included 320 eyes of 182 patients treated with either IVTA 4 mg or with the dexamethasone intravitreal implant for macular edema. The main outcome measures were the presence of elevated intraocular pressure (IOP) requiring treatment and the need for glaucoma surgery. Investigators calculated the relative risks for IOP-lowering treatment with the 2 steroid therapies.

No significant differences in visual acuity outcomes between the 2 steroid modalities were seen, but there was a difference in terms of safety. The dexamethasone implant had a safer side effect profile, with a lower risk of IOP elevation and a lower rate of surgical intervention required. No significant difference in the need for cataract surgery was seen. These results may reflect the differences in pharmacodynamics between bolus and device delivery mentioned above.

SHASTA STUDY

The recently published SHASTA study¹⁰ was performed to evaluate the efficacy, safety, and reinjection interval of the dexamethasone intravitreal implant in BRVO and CRVO in patients receiving 2 or more implants. This multicenter retrospective chart review included data from 289 patients at 26 sites, from baseline through 3 or 6 months after the last implant. The primary efficacy endpoint was change in BCVA from baseline.

Patients were divided fairly equally between BRVO (54%) and CRVO (46%). Notably, about 15% of patients had a history of IOP response to steroid, about 30% of patients had a diagnosis of glaucoma, and almost 25% were taking IOP-lowering medications.

These patients with IOP response and diagnosed glaucoma received the dexamethasone implant not just once, but twice or more. This kind of patient would not have been included in a prospective clinical trial, so this retrospective study gives us an opportunity to see the effect of the implant in a patient population that reflects real life in our clinics, to see how well these patients can be managed.

Another factor to remember is that, in patients with RVO, the best results of treatment are seen in those who have had macular edema for the shortest amount of time. In BRAVO, 67% of patients had macular edema secondary to BRVO for less than 90 days. In the SHASTA patient population, by contrast, the median duration of macular edema was 18.4 months. This is a pretty tough crowd.

All patients in SHASTA had at least 2 dexamethasone implants (range, 2 to 9), and the mean was 3.2 implants. The mean time between injections of the implants was 5.6 months (169 days; range, 81-527 days). That is a wide range, indicating that the implant is compatible with an individualized treatment approach. Treatment can be based on how the patient responds and how the disease progresses, rather than set schedules of implant injections.

The time between first implant and next anti-VEGF injection was also prolonged (24% at ~4 months, 12% at ~5 months, and almost 40% at more than 6 months) indicating that this combination approach is a more sustainable way of treating patients. The 2 treatments appeared to be nicely complementary.

Gains in visual acuity were impressive, with 62.9% of patients gaining 2 or more lines and 48.1% gaining 3 or more lines at final follow-up; 59.7% of BRVO and 66.7% of CRVO patients achieved a 2-line or greater improvement in BCVA. Figure 2 shows the percentage of patients with ≥ 3 lines improvement after each injection. Even in patients with 6 or more implants, there was improvement over baseline visual acuity with each injection, and likewise there was improvement in central retinal thickness with each injection compared with baseline.

A decrease in central retinal thickness to less than 250 μm achieved in 65.3% of total patients (BRVO 66.0%, CRVO 64.4%). Figure 3 shows the average change in central retinal thickness from baseline after each injection.

For 14% of patients, the dexamethasone implant was used as first-line treatment, with no previous interventions for RVO. For 29% of patients, the first dexamethasone implant was the last treatment they needed.

Regarding safety, IOP increases and cataract progression were the only treatment-related adverse events, with an incidence of 2% or more. Cataract surgery was required in 46 patients, but 85% of these patients had some degree of lens opacity at baseline. There was 1 report of endophthalmitis during the study, and there were no deaths or serious adverse events related to treatment.

Glaucoma surgery was required in 1.7% of patients, laser in 1.4%, and IOP-lowering medicines in 29.1%. In 7.3% of patients, an IOP of 30 mm Hg or more was recorded at any study visit.

At the final study visit, 4.3% of patients had a change in IOP from baseline of 10 mm Hg or more. An incidence of less than 5% despite repeated injections of the steroid implant suggests that these types of complications are manageable.

To summarize the notable SHASTA results, visual acuity improved by 2 lines or more in 63% of patients, despite a median duration of 18.4 months of macular edema. The average improvement in central retinal thickness on OCT was approximately 200 μm following the dexamethasone implant in this challenging patient population. Almost 70% of patients received the dexamethasone implants 4 to 6 months apart. At baseline, 31.5% of patients had a diagnosis of glaucoma or ocular hypertension, and 15.6% had a history of IOP response to steroids, but fewer than 5% of patients had clinically elevated IOP at their final visit.

CONCLUSIONS

The clinical use of 2 or more dexamethasone implants, either alone or in combination with anti-VEGF treatments, is safe and effective in the treatment of macular edema following BRVO or CRVO if IOP increases are monitored and treated. Decreases in macular edema and improvements in visual acuity were maintained with ongoing dexamethasone implant treatment. No new safety concerns developed after the use of multiple implants. Importantly, there was no evidence of a cumulative effect of repeat dexamethasone injections on IOP. ■

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1. Campochiaro PA, Heier JS, Feiner L, et al; BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010;117(6):1102-1112.
2. Jonas JB, Kreissig J, Degenring RF. Intravitreal triamcinolone acetonide as treatment of macular edema in central retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:782-783.
3. Scott IU, Ip MS, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein

- occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study report 6. *Arch Ophthalmol*. 2009;127:1115-1128.
4. Ip MS, Scott IU, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study report 5. *Arch Ophthalmol*. 2009;127:1101-1114.
5. Jain N, Stinnett SS, Jaffe GJ. Prospective study of a fluocinolone acetonide implant for chronic macular edema from central retinal vein occlusion: thirty-six-month results. *Ophthalmology*. 2012;119:132-137.
6. Boyer D. Ozurdex Diabetic Macular Edema Study. Paper presented at: 2013 Annual Meeting of the American Academy of Ophthalmology; November 16-19, 2013; New Orleans, LA.
7. Bhisitkul RB, Campochiaro PA, Shapiro H, Rubio RG. Predictive value in retinal vein occlusions of early versus late or incomplete ranibizumab response defined by optical coherence tomography. *Ophthalmology*. 2013;120(5):1057-1063.
8. Brown DM, Campochiaro PA, Singh RP, et al; CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010;117(6):1124-1133.
9. Chee DC, Edwards P, Ahmed S, Kahook K, Prinzi R. Comparison of complications and efficacy of dexamethasone intravitreal implant and intravitreal triamcinolone for macular edema. Poster presented at American Society of Retina Specialists annual meeting; August 24-28, 2013; Toronto.
10. Capone A Jr, Singer MA, Dodwell DG, et al. Efficacy and safety of two or more dexamethasone intravitreal implant injections for treatment of macular edema related to retinal vein occlusion (Shasta study). *Retina*. 2014;34(2):342-351.

Balancing Use of Intravitreal Steroids With Concerns About Intraocular Pressure Control

Putting the risk of glaucoma into perspective.

BY DENNIS P. HAN, MD

Intravitreal corticosteroid therapy has been shown in randomized clinical trials to offer potential benefits in numerous posterior segment pathologies, including macular edema (ME) due to retinal vein occlusions (RVOs), diabetic macular edema (DME), and chronic idiopathic uveitis.¹⁻⁵ Steroids can be delivered to the posterior segment by several methods, including intravitreal injection and a number of durable implants for long-term delivery.

Despite demonstrations of efficacy in multiple clinical trials, intravitreal corticosteroid therapy may be currently underutilized because of a fear of adverse events among clinicians that is disproportionate to the risks posed by these therapies.⁶

Many physicians may struggle to weigh the risk of intraocular pressure (IOP) elevation in their patients against the benefits to be derived from intravitreal steroids. The aim of this paper is to provide a perspective on the risk of glaucoma with intravitreal corticosteroid therapy. The more clearly clinicians can understand this issue, the better the care they can provide to their patients.

CASE REPORT

Consider the following patient, encountered early in the era of intravitreal therapy. A 54-year-old phakic man was referred with nonischemic central RVO (CRVO). Systemic workup was negative. The patient was treated with the

oral nonselective phosphodiesterase inhibitor pentoxifylline in an effort to reduce the ME associated with his CRVO. Despite treatment, the patient's vision worsened over several months from 20/25 to 20/100, with the development of 4+ cystoid macular edema (CME).

The patient elected to enter the SCORE trial assessing the use of intravitreal triamcinolone acetonide (IVTA) for treatment of CRVO,¹ which was enrolling patients at the time (2007). At the time of enrollment, his central subfield thickness on optical coherence tomography (OCT) was 928 μ m (Figure 1).

The patient responded well to treatment with IVTA, with resolution of much of the ME. However, the trial specified intervals of 4 months between injections. At 4 months after his second injection, although the patient's vision had improved to 20/60, he had recurrence of ME (Figure 2). Of note, the patient's IOP at this visit was 17 mm Hg, and his lens was clear.

This case illustrates that, although a treatment such as IVTA can safely improve visual function, sustained therapy is necessary for a chronic condition such as CRVO.

STERIOD TREATMENT OPTIONS

Each method of steroid delivery has unique risk and benefit characteristics.

One of the first steroid therapies widely employed for ophthalmic applications was IVTA. Commonly used

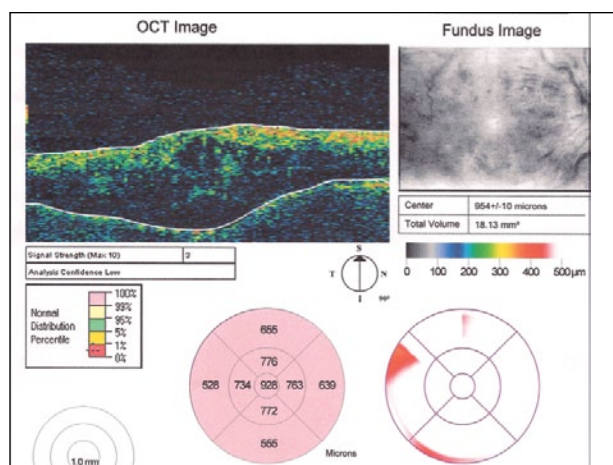


Figure 1. At the time of the patient's enrollment in the SCORE trial, central subfield thickness on OCT was 928 µm.

TABLE 1. IOP ELEVATION IN PERSPECTIVE

Agent	Topical control	Surgery
IVTA	20-35%	1% at 2 years (DRCR.net ¹)
Dexamethasone implant .7 mg	24%	0.7% at 6 months ²
Retisert fluocinolone implant	70%	37% at 3 years ³
Iluvien fluocinolone implant	0, 29% (.2 vs .5 mcg/d)	5% at 1 year ⁴
Ranibizumab	9%	0.2% at 2 years (DRCR.net ¹)

intravitreal doses are 1 mg and 4 mg, and the treatment effect can last 3 to 5 months. A preserved formulation of IVTA (Kenalog, Bristol-Myers Squibb) has been used by ophthalmologists for many years. More recently, 2 unpreserved preparations specifically formulated for ophthalmologic use as injectable suspensions have become available (Triesence, Alcon; Trivaris, Allergan). Although both of these agents are labeled for ophthalmic use, the vitreoretinal conditions for which they are most frequently used, including DME and ME secondary to RVO, are off-label indications.

A dexamethasone 0.7 mg intravitreal implant (Ozurdex, Allergan) is available. This biodegradable implant, inserted in an office-based procedure, provides 6 weeks of sustained release delivery with a total dose of 0.7 mg. It is said to have a biphasic release, with lower therapeutic levels persisting for up to 6 months. The dexamethasone implant is labeled for use in ME secondary to RVO and in noninfectious posterior uveitis.

There are 2 sustained-release devices containing fluocinolone acetonide (FA). The 0.59 mg FA intravitreal implant (Retisert, Bausch + Lomb) is sutured in place to deliver sustained release of FA for more than 30 months. It initially releases about 0.6 µg of drug per day, decreasing gradually over 30 months to 0.3 µg to 0.4 µg per day. This implant is labeled for treatment of noninfectious posterior uveitis.

The other FA implant (Iluvien, Alimera Sciences) is not

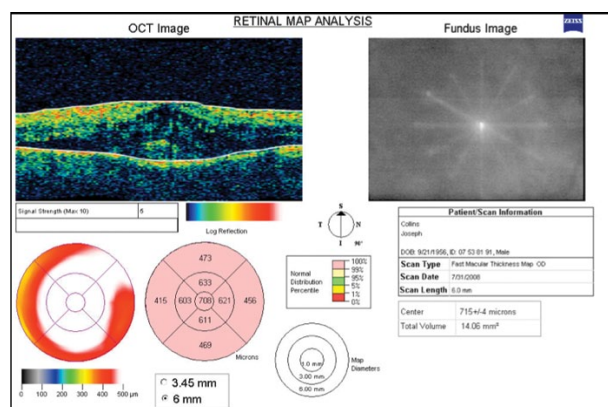


Figure 2. At 4 months after his second injection, although the patient's vision had improved to 20/60, he had recurrence of ME.

yet approved by the US Food and Drug Administration or commercially available in the United States, but it is approved in Europe and in use in several European countries. This device provides sustained release of 0.2 µg to 0.5 µg FA for a period of 2 to 3 years. It is inserted in an office-based procedure with an injector system, similar to the dexamethasone implant.

WHAT ARE THE RISKS?

In general, the risks of sustained intravitreal corticosteroid therapy include reactivation of latent infection, such as a viral or toxoplasmic retinitis; cataract development or progression; and IOP elevation.

Activation of infection is rare, but it has been reported.⁶ Cataract is a well-known risk, but the surgical results of cataract extraction are predictably good. The development of IOP elevation with sustained intraocular steroid use is relatively common, and this is the complication that is of most concern to clinicians.

Table 1 shows the need for IOP-lowering therapies, both medical and surgical, in clinical trials of the intravitreal steroid therapies described above. The figures are not directly comparable because they are taken from different studies with different designs, but they give some perspective on the risk of IOP elevation with these therapies.

Topical IOP control was needed in 20% to 35% of patients with DME treated with IVTA in a trial by the Diabetic Retinopathy Clinical Research Network.⁴ The rate of incisional glaucoma surgical intervention in that trial was 1% at 2 years in patients receiving IVTA.

In a trial assessing the dexamethasone 0.7 mg implant, 24% of patients received topical IOP control, and 0.7% needed incisional surgery at 6 months.³ With the 0.59 mg fluocinolone implant, which releases a relatively high amount of drug for a long period of time, a high percentage of patients received topical IOP control (70%), and there was a high rate of filtering surgery by 3 years (37%).⁷ The other FA implant, which releases smaller amounts of drug

per day, had a glaucoma surgery risk of 5 percent at 3 years.⁸

By comparison, patients with RVO receiving ranibizumab (Lucentis, Genentech)—an alternative, nonsteroidal treatment for DME—in the BRAVO trial needed topical treatment less frequently (9%), but a few patients (0.2%) still needed glaucoma surgery by 2 years' follow-up.⁹

The risk of severe adverse events associated with filtering surgery can influence the choice of therapy, but the incidences of these events are low. Expulsive hemorrhage occurs in about 0.01% to 0.15% of cases,¹⁰ and acute endophthalmitis in 0.06% to 0.2% of cases.¹¹

In the Tube Versus Trabeculectomy (TVT) Study, bleb-associated endophthalmitis was reported in about 1% of patients receiving the tube and 3% of those undergoing trabeculectomy.¹² By comparison, in patients receiving ranibizumab injections for DME, the endophthalmitis rate was 1% over 2 years.⁴

OTHER FACTORS THAT AFFECT DECISION-MAKING

Aside from reported safety and efficacy profiles, there are other factors that affect decision-making in the choice of therapies, including predictability, the availability of alternatives, cognitive bias, and manageability.

Predictability. A topical corticosteroid challenge prior to IVTA injection may be of limited value. Studies have shown a 40% chance that IOP will rise after IVTA injection despite a negative challenge test with topical therapy.¹³ Therefore, predicting which patients will not experience IOP elevation with intraocular steroids is difficult. I personally do not do a topical challenge. I just decide whether a patient needs the antiinflammatory treatment, and I assume that any resulting IOP elevation will be treatable, most likely with topical therapy. This makes the issue of predictability moot.

Alternatives. In general, anti-VEGF agents carry less risk of IOP elevation or cataract development, but more frequent injections are often required to achieve sustained benefit in ME. With respect to uveitis, the alternative to steroids is systemic immunotherapy. These agents introduce the risk of systemic toxicities and the need for monitoring.

Cognitive biases. Physicians and patients encounter a number of cognitive biases when thinking about the possibility of toxicity or complications associated with a treatment. One of these is omission bias: That is, the clinician and patient focus on what could happen, rather than what is most likely to happen following initiation of a treatment.¹⁴ Certain patients balk when any kind of treatment risk is mentioned, and physicians can sometimes do this too.

Another type of omission bias occurs when physicians underutilize a preventive intervention in order to avoid having a direct role in bad outcomes.¹⁵ For example, a physician might view visual loss from a natural cause—letting a disease take its course—as better than visual loss from an iatrogenic cause. So the physician might avoid

prescribing a treatment, even though the odds of a good outcome would be better if he did prescribe the treatment. This bias may govern behavior especially when vision loss is not imminent—for instance in a patient with an indolent ME without a risk of sudden blindness.

Regarding the risk of glaucoma surgery as a complication of corticosteroid therapy, one may consider 2 alternative perspectives. One might take the position that glaucoma surgery should be avoided, and therefore a treatment that could lead to glaucoma surgery—corticosteroid therapy—should also be avoided, even if loss of visual function is likely without that treatment. As an alternative perspective, one might say that glaucoma surgery can be an adjunct to an effective medical therapy that is needed to preserve visual function.

CLINICAL SCENARIO

I opened this article with a case example, and it may be instructive to close with another clinical scenario. What would you do in the following situation?

A patient presents with increased IOP despite maximum medical therapy, with the presence of residual intravitreal steroid from IVTA injection. Would you perform vitrectomy to remove the steroid? Or would you perform an aqueous shunt procedure?

Some might choose the aqueous shunt to allow future corticosteroid therapy to preserve visual function. If vitrectomy is performed to remove the steroid, one has to consider what problem is actually being treated. Are you treating the elevated IOP, or are you treating to preserve visual function?

This issue and its repercussions and ramifications prompted an editorial that I coauthored with Dale Heuer, MD.¹⁵ We closed with the following:

“If intravitreal corticosteroid therapy is deemed appropriate, the physician should proceed with the knowledge that its risks are manageable and that visual outcome, not IOP, should be the final arbiter in the decision making process.”

In the final analysis, we must consider the risks, benefits, and alternatives of corticosteroid therapy in each patient individually: Is it appropriate and are its potential complications manageable? We must be careful not to let the “tail” of elevated IOP “wag the dog” of preserving visual function. ■

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1. Ip MS, Scott IU, VanVeldhuisen PC, et al; SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Arch Ophthalmol*. 2009;127(9):1101-1114.

2. Scott IU, Ip MS, VanVeldhuisen PC, et al; SCORE Study Research Group. A randomized trial comparing the efficacy

and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol*. 2009;127(9):1115-1128.

3. Haller JA, Bandello F, Belfort R Jr, et al; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146.e3.

4. Elman MJ, Aiello LP, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064-1077.e35.

5. Jaffe GJ, McCallum RM, Branchaud B, Skalak C, Butner Z, Ashton P. Long-term follow-up results of a pilot trial of a fluocinolone acetonide implant to treat posterior uveitis. *Ophthalmology*. 2005;112(7):1192-1198.

6. Saidel MA, Berreen J, Margolis TP. Cytomegalovirus retinitis after intravitreal triamcinolone in an immunocompetent patient. *Am J Ophthalmol*. 2005;140(6):1141-1143.

7. Goldstein DA, Godfrey DG, Hall A, et al. Intraocular pressure in patients with uveitis treated with fluocinolone acetonide implants. *Arch Ophthalmol*. 2007;125(11):1478-1485.

8. Alimera Announces Positive 36-Month Results From the Completed Phase 3 FAME™ Study of ILUVIEN® in Patients With Diabetic Macular Edema [press release]. Alimera Sciences. February 3, 2011; Atlanta, GA. <http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=547652>. Accessed March 12, 2014.

9. Campochiaro PA, Heier JS, Feiner L, et al; BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010;117(6):1102-1112.e1.

10. Jiraskova N, Rozsival P, Pozlerova J, Ludvikova M, Burova M. Expulsive hemorrhage after glaucoma filtering surgery. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2009;153(3):221-224.

10. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) Study after five years of follow-up. *Am J Ophthalmol*. 2012;153(5):789-803.

11. Eifrig CW, Flynn HW Jr, Scott IU, Newton J. Acute-onset postoperative endophthalmitis: review of incidence and visual outcomes (1995-2001). *Ophthalmic Surg Lasers*. 2002;33:373-378.

12. Kempainen RR, Migeon MB, Wolf FM. Understanding our mistakes: a primer on errors in clinical reasoning. *Med Teach*. 2003;25(2):177-181.

13. Hollands H, Seif G, Hollands S, Gale J. A trial of topical prednisolone acetate before intravitreal triamcinolone acetonide decreases intraocular pressure spikes. *Can J Ophthalmol*. 2010;45(5):484-488.

14. Elstein AS. Heuristics and biases: selected errors in clinical reasoning. *Acad Med*. 1999;74(7):791-794.

15. Han DP, Heuer DK. Intravitreal corticosteroid therapy: putting the problem of glaucoma in perspective. *Arch Ophthalmol*. 2012;130(3):380-382.

Treating Cystoid Macular Edema With Steroid: Case Reports

BY ROBERT NOECKER, MD, MBA

Many glaucoma patients can tolerate steroid therapy without incident. Up to 50% of the population, however, has the probability of problems with steroids.¹ As clinicians, we do not have a consensus on treatment, but we must continue to closely monitor outcomes and be vigilant about treating those who may develop complications relating to steroid treatment. In this article, I will present 2 cases that help illustrate the difficulty these patients can pose, and how positive outcomes can be achieved with careful monitoring.

A CASE OF POSTOPERATIVE CYSTOID MACULAR EDEMA

A 60-year-old black woman presented with decreased vision several months after cataract surgery with multifocal IOL implantation. The patient had a history of early primary open-angle glaucoma that had been successfully managed with latanoprost. Family history noted the patient's mother had glaucoma that resulted in surgical treatment. This patient presented with a visual acuity of 20/25 in the right eye (OD) and 20/80 in the left eye (OS). She developed postoperative cystoid macular edema (CME) after her cataract surgery.

The patient had some early nerve fiber layer changes, and her visual fields were fairly good. The progression analysis showed a slow decline and probably glaucoma in both eyes, but her case was not too severe. Nonetheless, because of her glaucoma history, we did not want to take the "wait and see" approach with the CME as we might in a nonglaucomatous patient.

After 1 month of therapy with a nonsteroidal anti-inflammatory drug (NSAID) and a topical steroid, her

intraocular pressure (IOP) rose to 19 mm Hg OD and 38 mm Hg OS. Slit-lamp examination showed trace cells in the anterior chamber but was otherwise normal. A fundus examination revealed a cup-to-disc ratio of 0.8 in both eyes with somewhat improved CME in the left eye. The patient's difluprednate was changed to fluormetholone, and ketorolac drops were continued. We changed her latanoprost to fixed-combination timolol/brimonidine twice a day.

The patient continued to maintain an IOP of 19 mm Hg in the right eye and improved IOP of 18 mm Hg in the left eye, with trace cells in the anterior chamber and a visual acuity of 20/30 in the left eye. Her medical regimen was continued for 2 more months with improvement in both eyes to 20/25 and an IOP of 18 mm Hg in each eye.

DISCUSSION: CASE OF POSTOPERATIVE CYSTOID MACULAR EDEMA

Prostaglandin analogues by themselves do not cause inflammation or CME.²⁻⁵ Some studies have indicated that patients on latanoprost after routine cataract surgery have persistent flare over time that does not respond to antiinflammatory therapy. For instance, 1 study found that persistent flare seems to occur more frequently with latanoprost treatment than in patients who are treated with other prostaglandins.⁶ It is unclear as to the relationship between flare and latanoprost; perhaps there is a persistence of the breakdown of the blood-aqueous barrier in some of these patients.

I tend to stop prostaglandin analogues at the time of surgery if a patient is on an antibiotic, a steroid, and an NSAID, because the risk for complications can be higher.

CASE PANEL DISCUSSION

Dr. Varma: In my experience, it is only if prostaglandin analogues are prescribed more than once a day that the effects mentioned in your case report of postsurgical CME occur.

Dr. Noecker: Yes, and we saw this phenomenon happen in some of the early clinical trials with prostaglandin analogues where more than once daily dosing caused issues.

Another important consideration in these situations is the different potencies of steroids. When the more potent topical steroids are used, different responses occur, just as with the intravitreal formulation. When we switched this patient to a less potent steroid and kept her on nonsteroidal therapy, we basically eliminated the problems.

Dr. Singh: What's your opinion of difluprednate as far as IOP elevation goes? I find when you go beyond the twice-a-day dosing, an IOP spike definitely occurs.

Dr. Noecker: Elevation definitely happens more, especially in a closed system surgery such as cataract surgery. That said, I use it for cataract surgery because it is well known and very effective. After glaucoma surgery, there is a tube or hole in the eye, difluprednate can be used safely due to the improved outflow of aqueous from the eye. Difluprednate is extremely effective in suppressing cell migration and inflammation.⁷

A CASE OF CHRONIC BILATERAL CYSTOID MACULAR EDEMA

The second case is a 41-year-old male construction worker with chronic bilateral CME from vasculitis. He was referred from a retinal specialist after serial injections of steroids and anti-VEGF agents.

The patient then started a series of intravitreal triamcinolone acetate (Kenalog, Bristol-Myers Squibb) injections. After treatment, he presented with an IOP in the 40 mm Hg range and a visual acuity of 20/200 in both eyes (mostly from the macula issues). There was no glaucomatous optic nerve damage noted and no history of glaucoma. It was evident that this was ocular hypertension induced by steroids. He was at a high risk for damage, even though his initial IOPs had been normal.

The patient's CME was treated with maximal medical therapy to lower IOP with an unsuccessful result.

In this particular patient, after a month or so of trying numerous different medication combinations

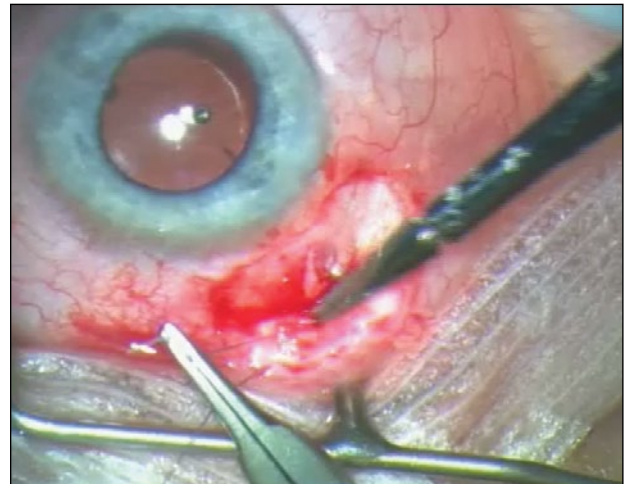


Figure 1. Bilateral chronic CME; a second tube shunt was placed, bringing the IOP under control.

but with IOPs still in the low 30 mm Hg range, we decided to implant an Ahmed glaucoma valve (New World Medical). This intervention worked well for 3 or 4 months. Additionally, the patient received intravitreal triamcinolone injections, which started to help his CME. Unfortunately, after a period of time his pressure started to rise again.

A preexisting tube had entered the iris, and although the valve was somewhat functional, the patient was developing a cataract. Most likely, the lens was getting thicker and was pushing the tube to occlusion. The patient then developed a significant posterior subcapsular cataract. At this point, the patient was still on the topical steroid and anti-VEGF therapy.

Because he had a cataract and what appeared to be a total shutdown of valve flow, the patient underwent cataract extraction and subsequent inferonasal Baerveldt tube shunt (Abbott Medical Optics) implantation.

I prefer to implant the tube shunts into the sulcus for good positioning. We successfully repositioned the first tube and were able to implant a second tube (Figure 1). His IOP then was under control, having gone down to the mid-teens.

Post tube implantation, the patient's visual acuity improved to 20/50, and he was able to stop his glaucoma medications. We then implanted a dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan). Gradually, the edema resolved and the patient did not require any further intervention for IOP.

DISCUSSION: CASE OF CHRONIC BILATERAL CYSTOID MACULAR EDEMA

This case reinforces our belief from a glaucoma specialist's perspective that intravitreal triamcinolone can cause IOP spikes. Anecdotally, we saw an epidemic of these spikes that would last several weeks and would

not respond to therapy when intravitreal triamcinolone started to be used en masse. ■

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1. Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group, Kempen JH, Altaweel MM, Holbrook JT, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. *Ophthalmology*. 2011;118(10):1916-1926.
2. Patel AS, Patel CC, Goyal A, et al. Impact of ocular hypotensive lipids on clinically significant diabetic macular edema. *Eur J Ophthalmol*. 2012;22(5):709-713.
3. Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. *Surv Ophthalmol*. 2008;53 Suppl1:593-105.
4. Yeom HY, Hong S, Kim SS, Kim CY, Seong GJ. Influence of topical bimatoprost on macular thickness and volume in glaucoma patients with phakic eyes. *Can J Ophthalmol*. 2008;43(5):563-566.
5. Chang JH, McCluskey P, Missotten T, Ferrante P, Jalaludin B, Lightman S. Use of ocular hypotensive prostaglandin analogues in patients with uveitis: does their use increase anterior uveitis and cystoid macular oedema? *Br J Ophthalmol*. 2008;92(7):916-921.
6. Miyake K, Ibaraki N, Goto Y, et al. ESCRS Binkhorst lecture 2002: Pseudophakic preservative maculopathy. *J Cataract Refract Surg*. 2003;29(9):1800-10.
7. Amon M, Busin M. Loteprednol etabonate ophthalmic suspension 0.5 %: efficacy and safety for postoperative anti-inflammatory use. *Int Ophthalmol*. 2012;32(5):507-517.

Steroids for Macular Edema: Case Reports

BY RISHI P. SINGH, MD

A CASE OF ANTI-VEGF NONRESPONSE

A 68-year-old man with a history of proliferative diabetic retinopathy (PDR) that was treated with prior panretinal photocoagulation (PRP) presented with a recent branch retinal vein occlusion (BRVO) with macular edema (ME). The patient had undergone bilateral IOL implantation and did not have a history of glaucoma.

Figure 1 shows the patient's fundus angiogram (FA) and optical coherence tomography (OCT) scans when I saw him 3 months prior and after the BRVO occurred. The arrow on the FA points to the area of the BRVO.

TREATMENT COURSE

The patient underwent 6 bevacizumab (Avastin, Genentech) injections over 7 months, with monthly evaluations to assess the response. Figure 2A shows his baseline spectral-domain optical coherence tomography (SD-OCT) and Figure 2B shows the SD-OCT after 6 injections. His baseline visual acuity was 20/50 and he only improved to 20/40 at 7 months. There was no significant response with regards to the visual acuity or the SD-OCT-measured retinal thickness. As a way to see whether the patient was responding to an anti-VEGF at all, I had the patient return 2 weeks after an injection for SD-OCT measurement of the retinal thickness. Even at 2 weeks, however, there was no difference, which is how I classified this patient as a nonresponder.

Figure 2C shows the change analysis for this patient. The intraocular pressure (IOP) range was between 23 and 25 mm Hg. With this in mind, I considered the

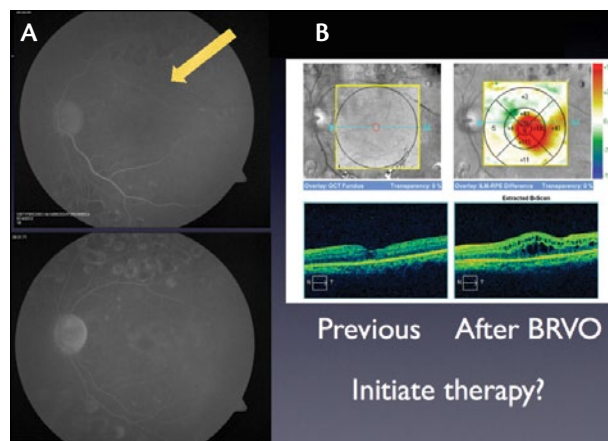


Figure 1. Case of VEGF nonresponse: Fundus angiography and OCT before (A) and after (B) BRVO.

options, which included switching anti-VEGF agents to ranibizumab (Lucentis, Genentech) or aflibercept (Eylea, Regeneron), intravitreal triamcinolone (Kenalog, Bristol-Myers Squibb), or the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan).

I decided to try a steroid and chose the dexamethasone implant because of its better safety profile. The patient responded well to the implant with a marked reduction in macular edema 3 months post implant injection and an improvement in visual acuity to 20/25 (Figure 3). The patient's IOP remained stable at 25 mm Hg. The patient did have a recurrence of edema after 6 months, and I reinjected with a second dexamethasone implant.

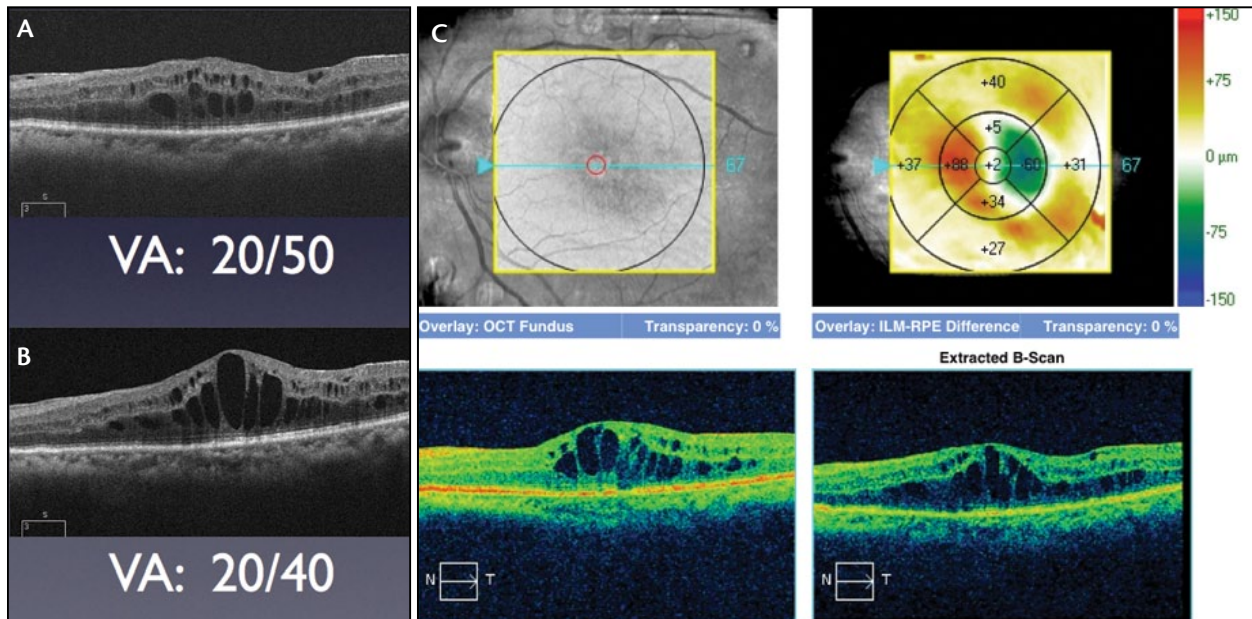


Figure 2. Baseline OCT (A) and OCT after 6 injections (B). Change analysis for the patient in case of anti-VEGF nonresponse (C).

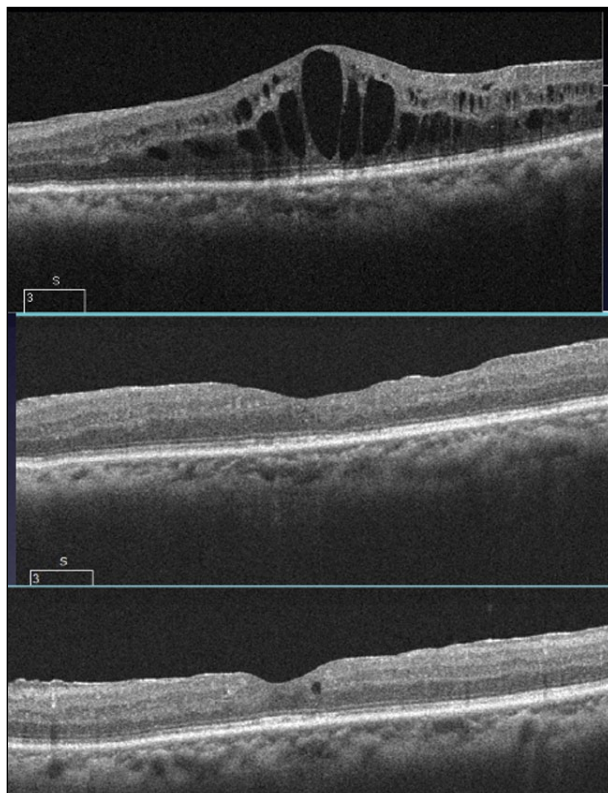


Figure 3. Case of anti-VEGF nonresponse: Marked reduction in macular edema 3 months post implant injection.

A CASE OF POSTOPERATIVE CYSTOID MACULAR EDEMA

A woman who had undergone previous vitrectomy for a dropped lens presented with significant cystoid macular edema (CME) postcataract surgery. She had under-

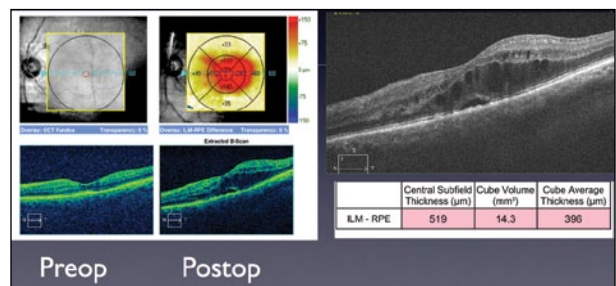


Figure 4. Case of postoperative CME: Recurrent CME postcataract surgery.

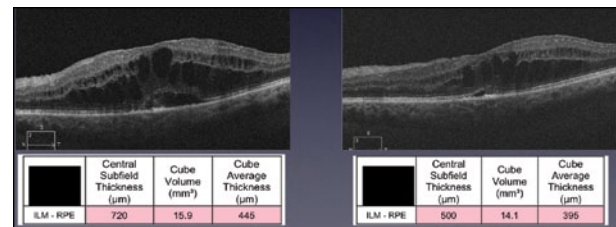


Figure 5. Case of postoperative CME: Modest improvement after topical therapy. There was no improvement in visual acuity.

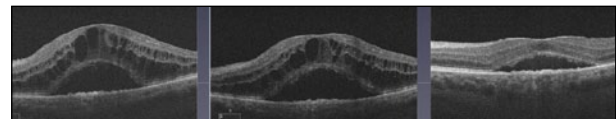


Figure 6. Case of postoperative CME: After injection with the dexamethasone intravitreal implant, the edema was reduced and visual acuity improved to 20/60.

gone Descemet stripping automated endothelial keratoplasty 3 months prior in her left eye, and her visual acuity has ranged between 20/150 and 20/200 in that eye. The

patient also had a history of glaucoma and Ahmed valve (New World Medical) placement, which lowered IOP down to 18 mm Hg. Figure 4 shows recurrent CME.

A topical steroid, such as prednisone or a nonsteroidal antiinflammatory drug is typically used for postsurgical macular edema and we used this approach. We saw a modest improvement in the central retinal thickness but no improvement in visual acuity (Figure 5). The patient could not continue with the topical therapy because she had developed severe arthritis, so I injected a dexamethasone implant. Over time, visual acuity improved and the edema

was reduced, so that at 3 months, her visual acuity was 20/60 and her OCT was remarkably better (Figure 6). Her IOP stayed in the range of 13 to 15 mm Hg. ■

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The Association of Steroids and Elevated Intraocular Pressure

Very few incidences of pressure rises require intervention.

BY ROHIT VARMA, MD, MPH

There are several distinctions between steroid-induced intraocular pressure (IOP) elevation and primary open-angle glaucoma (POAG). By definition, steroid-induced glaucoma is the elevation of IOP following the application of steroids with the subsequent development of optic nerve damage. Similarly, steroid ocular hypertension is the elevation of IOP following the application of steroids without evidence of optic nerve damage.

Aqueous exits the eye through the trabecular meshwork (Figure 1), which in turn acts as a sieve. In POAG, this sieve is in the juxtacanalicular area where there is a blockage in terms of aqueous outflow.

In steroid-induced elevated IOP, however, the spaces between the trabecular beams become plugged with glucosaminoglycans, which prevents aqueous from exiting through Schlemm canal.

HOW STEROIDS ELEVATE INTRAOCULAR PRESSURE

Unfortunately, no means yet exist to accurately predict which individuals will succumb to steroid-induced glaucoma. Even a slight elevation after the use of a topical steroid provides no guarantee that IOP will elevate with the use of intravitreal steroids.¹ There are, however, certain steroid-related characteristics and groups of people who are more likely to have elevated IOP. For instance, people who have experienced an IOP increase (or spike) of 15 mm Hg with a topical steroid are more likely to experience steroid-induced glaucoma.²

The more potent a steroid, the greater its antiinflammatory activity.³ If the steroid is delivered intravitreally or used for a longer period of time, it is more likely to

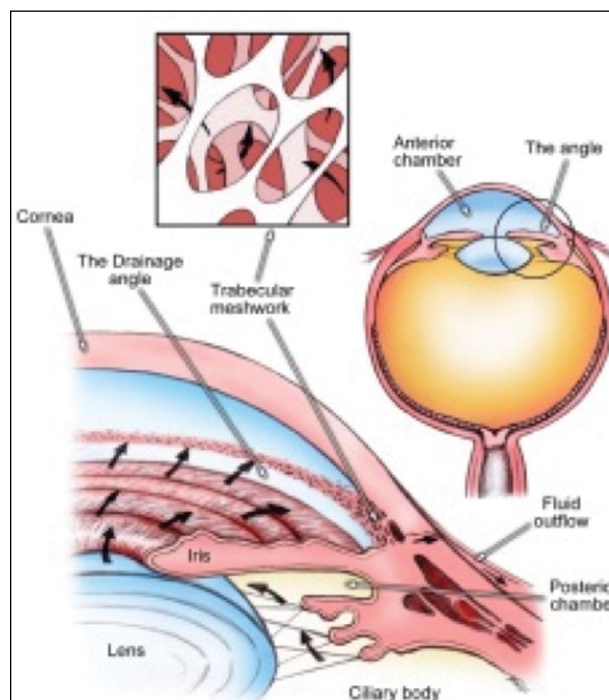


Figure 1. The mechanism of aqueous drainage.

cause an IOP elevation than a weaker steroid or one that is used for a shorter duration.⁴

In the posterior segment, 2 commonly used steroids are dexamethasone and triamcinolone acetonide. Figure 2 shows the average pressure rise of various steroids when used topically.

Patient history can provide an indication that someone may be at an elevated risk. Some commonly reported

IOP elevations for different steroids	
Preparation	Average pressure rise (mmHg)
Dexamethasone 0.1%	22.0 ± 2.9
Prednisolone 1.0%	10.0 ± 1.7
Dexamethasone 0.005%	8.2 ± 1.7
Fluoromethalone 0.1%	6.1 ± 1.4
Hydrocortisone 0.5%	3.2 ± 1.0
Tetrahydrotriamcinolone 0.25%	1.8 ± 1.3

Figure 2. Average IOP elevations for different steroids.

risk factors include POAG (or if a first-degree relative has POAG), glaucoma suspect, high myopia, type 1 diabetes, older age, and a previous steroid response. Again, previous steroid response is not a guarantee for subsequent response, but it should raise clinicians' awareness, particularly if the previous spike was 15 mm Hg or higher.

NATURAL HISTORY OF STEROID-RELATED INTRAOCULAR PRESSURE ELEVATION

Most steroid-induced IOP elevations are transient, lasting from a few weeks to a few months. The majority can be treated and controlled medically, but a small percentage of eyes will develop optic nerve damage and require surgical intervention.⁵

From a clinical perspective, if patients are elevation-free after 6 months, they will likely not have significant IOP issues going forward. Jonas et al⁶ described the natural history of steroid-related IOP elevation in patients dosed intravitreally with triamcinolone ranging from 7.8% in the first week to 20% to 25% between 4 and 8 months, dropping again to 7.3% at 9 months. The literature notes that up to half the patients experience an IOP rise up to a few months postinjection.⁷

TREATMENT ALGORITHM

There are several potential treatment algorithms when treating steroid-related IOP elevation. The underlying common determinate is that if retina specialists find that there has been an elevation of IOP, it is important to watch the patient for 6 to 9 months. Even if IOP was not elevated in the first month, IOP elevations after that time point can still occur, so my advice is to be cautious for the majority of that first year.

Figure 3 illustrates a quick reference differentiator between steroid-related glaucoma and POAG. Steroid-related glaucoma can occur at any age. In these patients, elevations can range from small amounts to pressures in the 50s, and can last up to a few months. However, these patients will rarely need surgical inter-

Steroid related Glaucoma vs. POAG		
	Steroid related glaucoma	POAG
Age of Onset	Any age	60+ years
Inciting event	Steroid use	None
IOP range	Teens to 50s	Twenties
Duration of IOP elevation	Weeks-months	Lifetime (decades)
Management	Topical medications	Topical medications, laser and surgery
Need for surgical intervention	Rare	Relatively common
Prognosis	Excellent	If detected early good. If detected late, poor

Figure 3. Steroid-related glaucoma vs primary open-angle glaucoma.

vention. Primary open-angle glaucoma, however, occurs in older individuals, has an unknown etiology, and the IOP elevation lasts for a lifetime. About half of POAG patients end up on 2 or more medications and may require additional interventions.⁷

SUMMARY

The following points should be considered when determining whether a patient is a suitable candidate for corticosteroids:

- (1) Elevation of IOP with steroid use is because of increased resistance to aqueous outflow, particularly in the trabecular meshwork.
- (2) Elevation of IOP is transient. It is in large measure related to how potent the steroid is and how it is introduced into the eye. Nonresponders to topical steroid administration may be responders to intravitreal administration of the same steroid.
- (3) Very few steroid-related elevations of IOP will need intervention or incisional intervention. The vast majority of individuals have an excellent prognosis and outcome. ■

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1. Bollinger KE, and Smith SD. Prevalence and management of elevated intraocular pressure after placement of an intravitreal sustained-release steroid implant. *Curr Opin Ophthalmol*. 2009;20:99-103.
2. Breusegem C, Vandewalle E, Van Calster J, Stalmans I, Zeyen T. Predictive value of a topical dexamethasone provocative test before intravitreal triamcinolone acetate injection. *Invest Ophthalmol Vis Sci*. 2009;50(2):573-576.
3. Kim SJ, Flach AJ, Jampol LM. Nonsteroidal anti-inflammatory drugs in ophthalmology. *Surv Ophthalmol*. 2010;55:108-133.
4. Jonas JB, Kreissig, Degenring R. Intraocular pressure after intravitreal injection of triamcinolone acetate. *Br J Ophthalmol*. 2009;87:24-27.
5. Kiddee W, Trope GE, Sheng L, et al. Intraocular pressure monitoring post intravitreal steroids: a systematic review. *Surv Ophthalmol*. 2013;58(4):291-310.
6. Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kamppeier BA. Intraocular pressure elevation after intravitreal triamcinolone acetate injection. *Ophthalmology*. 2005;112:593-598.
7. Reichle ML. Complications of intravitreal steroid injections. *Optometry*. 2005;76:450-460.

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CME QUESTIONS

1. The anatomic improvements achieved with ranibizumab in the BRAVO study, on average, plateaued at ____ month(s).

- a. 1
b. 3
c. 6
d. 12

2. The SHASTA study found that visual acuity improved by more than 2 lines in more than ____ of patients receiving the dexamethasone intravitreal implant.

- a. 52%
b. 35%
c. 64%
d. 45%

3. At baseline in the SHASTA study, ____ of patients had a diagnosis of glaucoma or ocular hypertension, and ____ had a history of IOP response to steroids, but fewer than ____ of patients had clinically elevated IOP at their final visit.

- a. 31.5%; 15.6%; 5%
b. 15.6%; 5%; 31.5%
c. 25.7%; 13.2%; 17.8%

4. Studies have shown a 40% chance that IOP will rise after IVTA injections despite a negative challenge test with topical therapy, making it difficult to predict which patients will have a pressure response to steroids.

- a. true
b. false

5. What percentage of the population has the probability of developing problems with steroid use?

- a. 15%
b. 28%
c. 50%
d. 82%

6. Optic nerve damage develops with:

- Neither steroid-induced glaucoma nor steroid ocular hypertension
- Steroid-induced glaucoma
- Steroid ocular hypertension
- Both steroid-induced glaucoma and steroid ocular hypertension

Did the program meet the following educational objectives?

I understand the potential for corticosteroid therapy to induce complications, including elevated IOP

I am able to distinguish between the different classes of corticosteroid therapy and relate the risks for complications associated with each

I am able to explain the early warning signs of elevated IOP

I am able to identify effective management strategies for patients requiring intervention

Agree Neutral Disagree

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Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME). Please complete the following course evaluation and return it via fax to FAX # 610-771-4443.

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