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The Intravitreal Use of Corticosteroids – Balancing Benefit and Risk

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The use of intravitreal (IV) corticosteroids was first explored 35 years ago and the enthusiasm for its use has waxed and waned over that time. While IV steroids will likely be supplanted by anti-vascular endothelial growth factor (VEGF) therapies as a primary treatment for retinal vascular diseases such as diabetic macular edema (DME) and retinal venous occlusive disease, the potent and largely unmatched anti-inflammatory properties of steroids will continue to make this a treatment of choice for conditions such as posterior uveitis. This issue of *Ophthalmology Rounds* reviews the pharmacology of different corticosteroid agents and drug-delivery systems, and presents the literature on the utility of steroids by disease entity.

The IV use of corticosteroids was first explored 35 years ago, when dexamethasone was proposed as adjunctive treatment for endophthalmitis.[1] Shortly thereafter, the potential benefit and safety of IV triamcinolone acetonide (TA) injection in preventing intraocular proliferation was explored in rabbits, with promising clinical results and no apparent safety concerns.[2,3] Over the following 20 years, IVTA was studied in diverse animal models of neovascularization and proliferative vitreoretinopathy,[4-6] and a 1995 pilot study proposed that it could play a role in the treatment of age-related macular degeneration (AMD) in humans.[7] It was soon noted that this treatment modality was associated with increased intraocular pressure (IOP) and cataract formation;[8,9] however, the promising short-term visual results prompted a large number of small studies of IVTA treatment for a wide range of retinopathies.

Pharmacology and Drug-delivery Systems

Corticosteroids have vasoconstrictive and antiproliferative effects, and are capable of inhibiting angiogenic growth factors and consequently preventing choroidal neovascularization.[10,11] They have also been shown to stabilize the blood-retinal barrier by increasing tight junction integrity, and to protect the retinal photoreceptors.[12,13] TA is a synthetic corticosteroid with anti-inflammatory potency 7 times higher than cortisone.[14] It is unclear which of its complex pharmacological functions is responsible for the clinical benefits observed after IVTA injection, but it is most likely a combination of effects that result in the observed reduction of fibrous proliferation and tractional detachments, inhibition of choroidal neovascularization (CNV), reduction in retinal arteriolar and venular diameters, improvement in macular function, and decreased leakage.[2,4,15,16]

The popularity that the IV use of TA has gained during the past few years can be attributed to several factors. First, it is a water-soluble drug, which can remain in the vitreous cavity longer than other steroids. Current evidence indicates that a 4-mg IVTA injection results in therapeutic levels in the vitreous for up to 3 months.[17] Second, TA is free of significant retinal toxicity when administered in standard or double concentration, and even doses as high as 25 mg appear to be well tolerated. Finally, the potent anti-inflammatory

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effect of TA offers a better risk:benefit ratio than other less clinically effective steroids, which nevertheless carry a similar risk of complications and toxicity.

One important issue that has received growing attention is the toxicity of commercially available TA preparations. Multiple studies have shown that benzyl alcohol, the preservative used in commercial suspensions, results in retinal toxicity.[18-20] It has been hypothesized that noninfectious inflammation, repeatedly reported after TA injections, may be attributed to the presence of a toxic preservative at unsafe concentrations. This theory is supported by reports of increased incidence of sterile endophthalmitis that decreased once a transition to preservative-free TA was achieved, and has resulted in an active pursuit of new suspension methods that would make it possible to avoid the use of toxic preservatives.[21-23]

Currently, injection is the only IV delivery method for TA. Various studies have been carried out to investigate diverse implantable devices or injectable systems; however, there is still no sustained-release product for TA available for clinical use in Canada. Implants are available for steroids other than triamcinolone, including dexamethasone and fluocinolone acetonide. A fluocinolone acetonide implant was approved in the United States (US) for treatment of noninfectious posterior uveitis, and provides sustained release of fluocinolone for up to 30 months. However, the device is associated with increased IOP in as many as 75% of eyes, and those requiring surgery had a higher risk of developing hypotony.[24] The dexamethasone drug delivery system (dexamethasone DDS), also approved in the US, contains 700 µg of dexamethasone and is inserted into the vitreous cavity. Dexamethasone DDS was well tolerated in a study of patients with ME and resulted in improved visual acuity (VA), macular thickness and fluorescein leakage in eyes with persistent edema.[25] Further to a high incidence of implantation-related complications, however, a new applicator system was developed,[26] consisting of a sterile, single-use instrument intended to deliver one preloaded dose of dexamethasone DDS into the vitreous humor via a 22-gauge needle, and resulted in a lower incidence of short-term complications, particularly vitreous hemorrhage. A ≥15-letter improvement was achieved by 40% of patients on day 90 of follow-up, and 20% maintaining the benefit for at least 180 days.[26]

Diabetic Macular Edema

DME is the most common cause of visual impairment in patients with diabetes mellitus. The current standard of care for clinically significant DME was established in 1985 after the Early Treatment Diabetic Retinopathy Study proved that focal/grid laser photocoagulation (GLP) of eyes with edema close to the fovea resulted in reduced 3-year vision loss as compared to observation.[27] However, the improvement in visual function offered by photocoagulation was limited, and an active search for more effective treatment options has taken place, particularly during the last 10 years.

Since corticosteroids have well-known anti-inflammatory properties and have also been demonstrated to inhibit the expression of VEGF, downregulate the VEGF gene, improve macular function, and narrow the retinal arteriolar and venular diameters,[28] their role in reducing DME seems promising and has been explored in a large number of clinical settings. IVTA as DME treatment gained rapid acceptance after initial results reported in 2001 and 2002 showed that it could be an effective therapeutic modality.[29,30] However, it also became apparent that the benefits offered by TA were transient, requiring frequent retreatments, which in turn increased the incidence of complications such as elevation of IOP and cataract development. The Diabetic Retinopathy Clinical Research (DRCR) Trial[31,32] demonstrated that focal/GLP is more effective and has fewer side effects than TA, and suggests that laser therapy should remain the benchmark against which other therapeutic modalities are to be compared. Recent studies have shown clinical benefits when combining IV steroids with anti-VEGF antibodies (bevacizumab) and laser photocoagulation.[33,34] It has also been determined that IVTA during pars plana vitrectomy (PPV) for diabetic vitreous hemorrhage is effective in preventing rebleeding.[35]

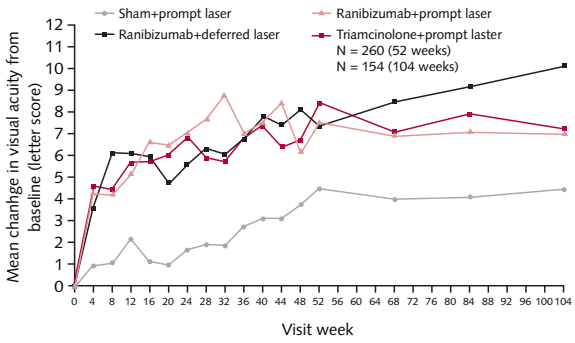
The DRCR Network[36] also evaluated anti-VEGF therapy (ranibizumab) alone or in combination with laser, TA in combination with laser, and laser alone in 854 eyes of 691 DME patients. They found that IV ranibizumab with prompt or deferred (≥24 weeks) focal/GLP had superior VA and optical coherence tomography (OCT) outcomes (+9 letter gain at 1 year) compared with focal/GLP treatment alone (+4 letters) or with the combination of laser and TA (+3 letters). While IVTA combined with focal/GLP did not result in superior VA outcomes compared with laser alone, in an analysis limited to pseudophakic eyes, the TA group's outcome for VA appeared to be more effective than laser alone and of similar magnitude to that of the 2 ranibizumab groups (Figure 1); however, the risk of IOP elevation was increased markedly.

In the case of persistent or refractory DME, a 2007 systematic review of 7 large trials (632 DME eyes) found a beneficial effect of TA injection and IV steroid implantation compared to standard of care.[37] Thus, IV steroids will most likely be reserved for treatment of cases of refractory edema, where safer therapeutic options are ineffective.

Central Retinal Vein Occlusion (CRVO)

Early small, retrospective studies found that IVTA improved the VA and reduced cystoid ME of CRVO

Figure 1: Mean Change in Visual Acuity at Follow-up Visits Among Eyes That Were Pseudophakic at Baseline.



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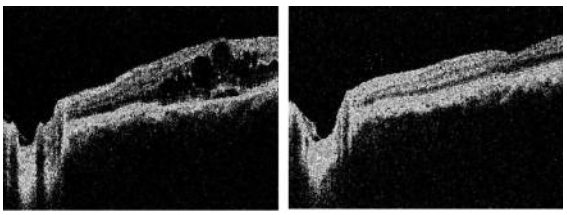
patients; however, the limited follow-up of 6 months on which the reports were based makes it impossible to draw definite conclusions about the efficacy of this treatment (Figure 2).[38,39] Wang et al[40] demonstrated that a second injection is less effective than the initial dose in reducing recurrent edema and restoring vision. Wu et al[41] found that IVTA and bevacizumab were equally effective in improving VA and temporarily decreasing ME secondary to CRVO, but that IVTA seemed to be associated with more complications.

The Standard Care versus COrticosteroid for REtinal Vein Occlusion (SCORE) study[42] (N=682) evaluated the benefits of IV steroids for occlusions involving the central or branch retinal veins. The odds of achieving the primary outcome (≥15 gain in VA letter score) with either dose (1 mg or 4 mg) of IVTA were 5 times greater than with observation. Due to the higher rate of complications with the 4-mg dose, the authors recommended 1 mg for up to 2 years in the treatment of CRVO-related ME.

Branch Retinal Vein Occlusion (BRVO)

The SCORE study for BRVO showed no difference in VA at 12-month follow-up between GLP and IVTA (1 mg and 4 mg).[43] The authors concluded that GLP should remain as the standard of care for patients with vision loss associated with ME secondary to BRVO.

Figure 2: Triamcinolone for the treatment of central retinal vein occlusion. Left: Optical coherence tomography of a patient with cystoid macular edema. Right: Six weeks after intravitreal injection of triamcinolone acetonide.



Age-related Macular Degeneration (AMD)

The role of IV steroids in treating exudative AMD has been explored in multiple studies since 1995. In particular, they showed some promise when combined with photodynamic therapy (PDT). The role of PDT with or without steroids, however, has been almost entirely supplanted by the intravitreal anti-VEGF agents, ranibizumab and bevacizumab, which have demonstrated superior efficacy and fewer adverse events.[44-46]

Noninfectious posterior uveitis

IV corticosteroids have been typically reserved for cases of cystoid ME (CME) secondary to uveitis that are refractory to standard treatment with topical or periocular corticosteroids.[47,48] Small studies have shown that IVTA improves both central macular thickness and VA, but its effect wears off after a few months, requiring repeated injection. Some patients do not respond to IVTA once the initial effect disappears, but it has been described that increasing the dose may offer additional benefit.[49,50]

In a small study (11 eyes of 9 subjects) investigating the efficacy of bevacizumab in patients with uveitic CME, Weiss et al[51] determined that IVTA, which was administered to bevacizumab nonresponders, is a better option than the anti-VEGF agent for patients with diffuse leakage from the choroid or optic disk.

Steroid implants have also been investigated in uveitis-related CME. Callanan et al[52] found that the fluocinolone acetonide implant reduced angiographic CME in up to 86% of patients with uveitic edema. Their 3-year multicentre, randomized study of the implant to treat posterior uveitis found a reduction in uveitis recurrence from 62% during the 1-year preimplantation period to 4%, 10%, and 20% at 1, 2, and 3 years postimplantation. Additionally, significant visual benefits were recorded, along with a diminished need for systemic immunosuppressive and anti-inflammatory therapy in nearly 80% of patients. The benefits were accompanied by higher incidence of elevated IOP and a need for glaucoma surgery in 40% and cataract surgery in 93% of implanted eyes. Williams et al[53] found that dexamethasone DDS provided significant improvements in VA and fluorescein leakage in uveitic ME patients; however, 5 of 13 subjects who received the dexamethasone DDS implant experienced an increase in IOP of ≥10 mmHg.

Pseudophakic ME

IVTA has produced mixed results in the management of refractory pseudophakic CME. Sørensen et al[54] reported a significant recovery of VA and anatomical

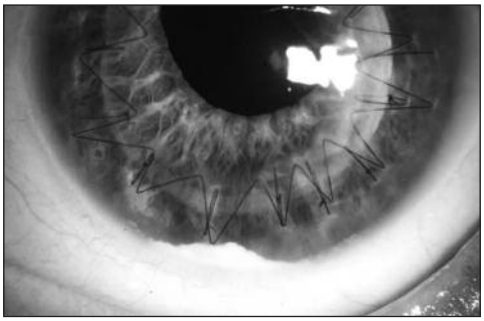
improvement, as documented by OCT and fluorescein angiography, whereas Boscia et al[55] reported no improvement. As seen with IVTA in other disease states, IOP was elevated in these 2 studies (32% and 57%, respectively).

Adverse Effects of IV Corticosteroids

Development of posterior subcapsular cataracts is the most frequent adverse event; after 3 years of IV steroid treatment, the rates are as high as 83%-93%.[31,52] Probably the most important complication associated with IV steroid use is elevated IOP, not only due to its high frequency, but also because its management may be complicated and adequate IOP control difficult to achieve. Gonioscopic changes characterized by pigmented particulate matter in the inferior angle have been described to accompany the IOP elevation, and have been documented to occur as early as 2 weeks after a single 4-mg TA injection.[56] Not surprisingly, elevated IOP is more common with higher doses. One-third of patients will experience an increase in IOP of ≥10 mm Hg, IOP-lowering therapy is required in approximately 12% of patients, and 4% will require glaucoma surgery over the first 3 years of IV steroid therapy.[32] The incidence of elevated IOP is higher (40%) with steroid implants.[52] A history of glaucoma has been identified as a strong risk factor for high IOP following IVTA injection, and is considered a relative contraindication to this form of treatment.

The incidence of infectious endophthalmitis associated with IV steroids is estimated to be <0.9%, with symptoms typically appearing within 8–14 days after treatment. Diabetes mellitus, multi-use TA bottles, filtering blebs, and blepharitis have been identified as possible risk factors, and *Staphylococcus* and *Streptococcus* tend to be identified as the invading microorganisms;[57] however, there have been reports of infection with atypical mycobacteria.[58] Most cases of post-IVTA endophthalmitis, however, are negative for the presence of microorganisms, with the overall incidence of sterile endophthalmitis reported as high as 1.6%. There have been reports of specific batch-associated clusters of cases, where as many as 9.3% of eyes treated develop sterile endophthalmitis (Figure 3).[59] The etiology behind this increased incidence has not been clarified, as analysis of the affected drug lot did not show contamination or bacterial endotoxins, but it has been speculated that the preservatives used in TA preparations, particularly benzyl alcohol, can be responsible.

Figure 3: Pseudohypopyon and sterile endophthalmitis following intravitreal triamcinolone injection.



The immunosuppressive nature of steroids may sometimes contribute to an activation or reactivation of previous intraocular disease, and recently 2 cases of acute syphilitic posterior placoid chorioretinitis have been described after IV injections of TA.[60] Cytomegalovirus retinitis has also been frequently reported in immunocompetent patients following IV steroid injection.[61-64]

Conclusions

Despite years of use for a variety of retinopathies, only recently has the evidence-based picture of the safety and efficacy of IV steroids begun to emerge. While it is obvious that they offer a clinical benefit, this does appear to be short-lived. The requirement for multiple retreatments increases the incidence of adverse effects, making the decision to proceed with IV administration of corticosteroids more difficult. Recent and soon to be completed randomized clinical trials will help inform that decision-making process when using these agents.

At this point, however, it appears as if combination therapies are most likely to play an important role in treating most causes of ME and neovascularization, and more studies will be needed to determine the right timing for initial and repeated treatment, as well as the optimal dosage and ideal candidates for maximum benefits.

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