

Injectable Intraocular Corticosteroids

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Core Messages

- Although risks are present, intravitreal corticosteroid injection is a relatively safe and effective treatment in a variety of conditions.
- Risks of intravitreal steroid injection include, but are not limited to, elevation of intraocular pressure, infection, cataract, retinal detachment, and central retinal artery occlusion.
- Although most observations regarding intravitreal corticosteroid injection derive from treating diabetic macular edema and age-related macular degeneration, this approach is beneficial in a number of uveitic conditions.

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This chapter contains the following video clip on DVD: Video 1 shows Injection of intraocular Corticosteroids (Surgeon: Christina J. Flaxel).

1.1 Introduction

Corticosteroids have been used to treat ocular inflammation since the 1950s [1]. Use of systemic corticosteroids subjects the patient to numerous side effects. Local therapy with drops or injections can minimize side

effects. Periocular or intravitreal injections can be particularly useful, if tolerated, in patients with unilateral disease that is not amenable to topical therapy alone. If systemic manifestations of the disease exist, or if ocular disease is bilateral and repeat injection, particularly frequently repeated intravitreal injection, is necessary, use of a systemic steroid-sparing immunosuppressive agent may be a better option.

Prednisolone acetate drops are often effective in cases in which the inflammation is restricted to the anterior chamber. However, adequate levels are not achieved in the vitreous cavity and retina. Periocular corticosteroid

injection can be useful in many cases of inflammation involving the posterior segment, but most experts find that intraocular delivery is more potent.

In the late 1970s, Machemer and McCuen established the safety of intravitreal triamcinolone acetonide (TA) and studied its effect on intraocular proliferation [2, 3]. Intravitreal injection has the advantage of delivering the drug more directly to the target tissue. However, a trade-off is increased risk of complications that arise from injection directly into the eye.

By the late 1990s, there was increased clinical study of intravitreal TA as a treatment for conditions including refractory macular edema and choroidal neovascularization [4–6]. Although the United States Food and Drug Administration has not approved this indication, intravitreal injection of TA became commonplace after 2002. With the advent of various intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, the use of TA has declined for treatment of neovascular age-related macular degeneration. However, it still remains a useful option in a number of conditions, many of which are uveitic.

1.2 Types and Formulations

While a number of forms of corticosteroids exist, in most cases triamcinolone acetonide is the preferred formulation for injection into the eye. It is a minimally water-soluble suspension and acts essentially as a depot of sustained-release crystals when injected into the vitreous cavity. This leads to a longer half-life compared to more water-soluble forms such as dexamethasone. In cases in which intraocular pressure (IOP) rise is a significant concern, a corticosteroid with a shorter half-life is sometimes used. This, in theory, may decrease the risk of prolonged IOP rise, but may also decrease the duration of effect.

Triamcinolone acetonide has been commonly purchased in single-dose vials at a concentration of 40 mg/ml. Some patients may have a sterile inflammatory reaction to the injection. This is thought to be due to an additive in the formulation rather than the triamcinolone itself. Various methods exist for purifying the drug for injection, and preservative-free formulations are now available. Centrifugation removes most benzyl alcohol and thus reduces potential toxic effects [7]. One retrospective study of 310 eyes that received intravitreal TA suggested that sterile inflammatory reactions may be more common in uveitic eyes than in eyes without an underlying inflammatory predilection. In this study, 4 of 20 uveitic eyes experienced a sterile inflammatory reaction. By contrast, only 2 of 290 eyes treated for non-inflammatory posterior segment disease developed this

complication [8]. This finding has not been validated by other investigators to date.

1.3 Doses

The typical dose injected in the United States is currently 4 mg. At the time of this writing, the SCORE (Standard of Care versus Corticosteroids for Retinal Vein Occlusion) Study is investigating the use of 1-mg versus 4-mg injections, versus placebo. In Europe, 25-mg injections have been used [9].

1.4 Distribution After Injection

In a study of 20 patients, following injection of a high dose (20–25 mg) of TA into the vitreous cavity, TA was not detectable in serum samples of 90% of the patients. Two patients showed marginally detectable amounts of serum TA, one at 5 days after injection and the other at 7 days after injection [1, 10].

Studies comparing the intravitreal concentration of TA after periocular injection to those after intravitreal injection have been performed. One study of vitreous samples from 12 patients, six of whom had intravitreal injection and six of whom had periocular injection, showed higher concentrations of TA after intravitreal injection [11]. A study by Thomas compared the intravitreal concentrations of TA after sub-Tenon injection in 20 patients versus that after intravitreal injection in 5 patients previously reported by Beer et al. The findings showed that, in some cases, intravitreal concentrations after sub-Tenon injection were comparable to those after intravitreal injection [1, 12].

1.5 Duration of Effect and Frequency of Injections

The duration of effect of intravitreal TA appears to be dose-dependent and is considerably shorter in vitrectomized patients. In the absence of vitrectomy, doses of 20 mg give a duration of effect of 6–9 months while the more typical dose of 4 mg shows a duration of effect of 4–6 months, although a longer duration can be seen [11]. Jonas showed that up to 8 months after injection of 25 mg of TA into eyes that had previous pars plana vitrectomy with silicone oil endotamponade, detectable levels of TA were present in extracted silicone oil samples [13].

Beer showed that after a single 4-mg injection, the mean elimination half-life was 18.6 days. In eyes that

had undergone vitrectomy, the mean elimination half-life was 3.2 days. However, considerable variation of peak concentration and half-life occurred among subjects. The range of measurable concentration of intravitreal triamcinolone in humans was 71–132 days. This is longer than the 42 days of measurable dexamethasone concentration $>1 \mu\text{g/ml}$ in rabbits after receiving a dexamethasone sustained delivery device (DEX-BDD, Posurdex™) [1].

Reinjection can be considered if necessary after the effect from the prior injection is likely to have faded. If clinical signs suggest worsening of a condition that had improved after the first injection, reinjection would ideally occur before more pronounced worsening. Obviously, the risk–benefit ratio of reinjection must be considered. Retreatment has been performed as often as every month to every 3–6 months [14].

1.6 Mechanism of Action

The exact mechanism(s) by which intravitreal TA has its effects is not fully known. Glucocorticoids appear to have a variety of actions, including inhibition of expression of genes contributing to inflammation and thus decreased production of cytokines, enzymes, receptors, and adhesion molecules [15]. They have been shown to interfere with fibroblast and endothelial cell function and reduce fluid transudation. In animal studies, they have been shown to inhibit neovascularization. Studies have also documented reduction of endothelial cell permeability and down-regulation of inflammatory markers [16–18].

A common use of intravitreal triamcinolone is for treatment of macular edema. It is thought that in most cases, macular edema develops following breakdown of the inner blood–retinal barrier. The breakdown of the outer blood–retinal barrier with disruption of the tight junctions between RPE cells may also play a role. TA stabilizes the blood–retinal barrier. It may also down-regulate the production of VEGF, which has been shown to be a vascular permeability factor that may be released by ischemic retina in diabetes mellitus. Inhibition of prostaglandins, which are known vascular permeability factors, may be an additional mechanism for reduction of macular edema [19, 20].

1.7 Risks

There are a number of risks associated with intravitreal TA injection. Explanation of these risks to the patient should be documented with a written informed consent.

The patient should be aware that further intervention may be needed, the problem may not be rectified, and that vision or even the eye could conceivably be lost as a result of the procedure. The patient should be warned to contact the ophthalmologist with any concerns and definitely for symptoms of worsening pain, worsening vision, increasing redness, flashes, and symptoms of retinal detachment.

1.7.1 Elevation of Intraocular Pressure

Corticosteroids taken by any route can increase intraocular pressure (IOP). Obviously, the most direct way for corticosteroids to produce ocular effects, both good and bad, is application directly into the eye. While in some cases of hypotony, the IOP-raising effect can be beneficial, in most cases it is an unwanted side effect. Elevated IOP can occur immediately after injection or develop up to 7 months after injection [21].

A study by Rhee et al. of 570 consecutive eyes of 536 patients who underwent intravitreal TA (4 mg/0.1 cc) revealed that a baseline IOP of greater than 16 was a risk factor for developing IOP elevation after intravitreal injection. In addition, receiving a second injection of TA increased the risk of IOP elevation. Of eyes receiving a single injection, 53.2% had IOP elevation. This included 50.6% experiencing an elevation of at least 30% of baseline, 45.8% experiencing an elevation of 5 mmHg or more, and 14.2% experiencing an elevation of 10 mmHg or more. Of eyes receiving a second injection, 65.1% experienced IOP elevation of at least 30% [22].

Cardillo et al. studied 12 patients with bilateral diabetic macular edema and randomly assigned one eye of each patient to receive 4 mg of TA intravitreally and the fellow eye to receive 40 mg of TA by posterior sub-Tenon's injection. Interestingly, IOP did not show any statistically significant difference between the two delivery routes at 1, 3, and 6 months. While a controlled IOP elevation was noted in a number of the treated eyes, no eyes in that study had an increase in IOP above 25 mmHg [23]. Another small study of 28 eyes in 28 patients showed a significant increase in the mean IOP at 4 and 8 weeks after sub-Tenon's TA injection, while there was a smaller but significant IOP increase in the intravitreal TA group at 8 weeks only [24]. Other larger studies have shown IOP rise in 27% [25] and 36% [26] after sub-Tenon's injection of TA. Hayashi's study of 60 patients showed the incidence of IOP rise to be less when 40 mg of TA was injected by retrobulbar route than when 4 mg was injected intravitreally [27].

A study of patients with uveitic CME suggested that younger patients are more likely to have IOP rise in response to intravitreal TA injection. In this study, an IOP

rise greater than 10 mmHg was more likely in patients younger than 40 years of age (61%) than in those older than 40 years of age (30%) [28].

Obviously patients who have had increased IOP in response to corticosteroids administered by another route in the past are more likely to have increased IOP in response to intravitreal corticosteroids. Depending upon the amount of IOP elevation and the ability to control the IOP in the past, intravitreal injection may still be a reasonable option.

Some advocate a trial with topical corticosteroid drops for several weeks prior to intravitreal injection to determine if patients are “steroid responders.” This may be beneficial in filtering out the patients likely to have the worst IOP responses but is certainly not foolproof. In addition, it would essentially delay the time to effective posterior segment treatment and, particularly in cases of macular edema (ME), earlier treatment may lead to better visual outcome. In one study, despite exclusion of patients who had a rise of IOP greater than 15 mmHg after 1 month of treatment with 0.1% dexamethasone drops, 50% of patients who received intravitreal TA had an IOP rise [29].

It is generally thought that patients with chronic open-angle glaucoma (COAG) are more likely to be steroid responders, although one study did not show any difference in postinjection IOP in patients with or without COAG. This may have been related to a small sample size of COAG patients [30].

In many cases of steroid responders, the IOP returns to normal as the duration of steroid effect is exceeded. However, IOP can remain persistently elevated. Some suggest that intractable glaucoma is more common after intravitreal TA in cases of macular edema due to central retinal vein occlusion (CRVO) than in other indications for intravitreal TA injection [18].

1.7.2 Infectious Endophthalmitis

Recent studies have reported the incidence of infectious endophthalmitis following intravitreal injection of TA to range from 0% (0/700) to 0.87% (8/992) [31]. Sterile technique can help reduce the risk of endophthalmitis. Particularly important is instillation of povidone-iodine drops (either 5% or 10%; the 5% solution is less irritating to the cornea and conjunctiva) directly onto the injection site prior to injection. Some also advocate use of an antibiotic drop (commonly a fluoroquinolone) just before the injection and 4 times a day for 3–5 days following the injection. Use of a single-injection vial of TA, or at least a brand new bottle, for each injection is also recommended. Based on animal studies, some have suggested that intravitreal methotrexate injection may re-

duce the risk of development of infectious endophthalmitis and may be a safer alternative to corticosteroid injection in the treatment of noninfectious uveitis [32].

Signs and symptoms of infectious endophthalmitis can develop at any time following intravitreal TA injection, but will typically appear by postinjection day 5. In one retrospective study of eight patients who developed postinjection endophthalmitis, the median time to presentation was 7.5 days. Characteristic symptoms were pain, redness, blurry vision secondary to iritis, vitritis, and/or hypopyon [33]. However, one must keep in mind that patients with infectious endophthalmitis following intravitreal corticosteroid injection may not experience the level of pain typically experienced in eyes without intraocular steroids [31]. Despite aggressive and early treatment, visual outcomes may be poor.

There is one report of de novo development of cytomegalovirus (CMV) retinitis in an immunocompetent patient who received intravitreal TA [34]. Thankfully this appears to be quite rare. There is also a report of CMV retinitis developing in a patient after a fluocinolone acetonide (Retisert™) implant. This patient had numerous periocular and intravitreal corticosteroid injections in the contralateral eye but only developed CMV retinitis in the eye with the fluocinolone acetonide implant [35].

1.7.3 Sterile Inflammatory Reaction

If a sterile inflammatory reaction develops, it typically does so within 2 days following intravitreal TA injection. This inflammatory reaction is thought to be a response to a chemical used in the formulation of TA. Typically, patients can present with symptoms similar to that of infectious endophthalmitis. However, visual outcomes are generally good [36]. Since preservative-free formulations of TA are used in the SCORE study, additional data on the incidence of infectious and noninfectious endophthalmitis plus data on the effectiveness and potential benefits of preservative-free formulations may soon be available [18].

1.7.4 Pseudoendophthalmitis

Pseudoendophthalmitis occurs when TA crystals move into the anterior chamber and form a “pseudohypopyon.” This occurs most often in pseudophakic and aphakic patients, although it has been described in phakic patients. The patients typically do not experience any pain and the pseudohypopyon resolves. The eye is frequently otherwise quiet.

1.7.5 Cataract

Corticosteroids are a well-known cause of cataract, particularly posterior subcapsular cataract (PSC). Thus, although increased visual acuity is often noticed relatively soon after intravitreal corticosteroid injection, over time, visually significant cataracts may form and may require cataract surgery.

A recent retrospective study of 93 eyes that received a 4-mg TA injection showed visually significant PSC formation in almost 50% by 1 year after injection. Patients younger than 50 years of age had about half the rate of progression compared to patients over 50. There were slight increases in the formation of nuclear sclerotic and cortical cataracts as well [21].

Another study of 33 eyes found that 2 years after injection, nuclear sclerosis increased in 9.1% of eyes, cortical cataracts increased in 12.1%, while PSC increased in 24.2% over that same time period. This study also found that PSC progression was much more frequent in eyes with at least a 5-mmHg rise in IOP [37, 38].

1.7.6 Retinal Detachment and Vitreous Hemorrhage

Retinal detachment and vitreous hemorrhage have been reported following intravitreal injection [39]. Conceivably, with introduction of triamcinolone into the vitreous, disruption of the vitreous could take place. This could lead to traction on the retina, retinal tears, and subsequent retinal detachment. In addition, if during the process of injection, traumatic damage occurs to the retina, retinal holes, retinal detachment, or vitreous hemorrhage may occur. These complications are rare, and in a recent study of 348 eyes by Jonas, none developed rhegmatogenous retinal detachment [30].

1.7.7 Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) may occur immediately following an intravitreal injection if the postinjection IOP is high enough to stop retinal artery perfusion. Careful examination to ensure retinal vessel perfusion should be done immediately following the procedure. If postinjection IOP is sufficiently high to prevent adequate retinal vessel perfusion, an immediate anterior chamber paracentesis should be performed to lower the IOP and allow reperfusion of the retinal vessels before permanent retinal damage and cell death from ischemia can occur. Intraocular pressure should be

documented soon after the injection and checked again in approximately 30 minutes to make sure the pressure is not rising and is at a safe level prior to discharging the patient home.

1.7.8 Central Serous Chorioretinopathy

Corticosteroids are known to exacerbate central serous chorioretinopathy (CSCR). Development of CSCR has been reported following vitrectomy with intravitreal TA [40]. It is unclear whether this represented a true cause-and-effect relationship. CSCR has also been reported with periocular corticosteroid injection treatment for HLA-B27-associated iritis [41].

1.7.9 Toxic Effects

Although the lack of toxicity of intravitreal TA has been documented in rabbits and widespread clinical use has proven beneficial in many cases, in vitro evidence for toxicity to human retinal pigment epithelium (ARPE-19) cells exists. At in vitro concentrations of 1 mg/ml, ARPE-19 cell viability was reduced to the greatest extent by the commercially available TA (including the vehicle preserved with benzyl alcohol), to a lesser extent by the vehicle alone, and least by preservative-free TA. While 1 mg/ml vitreous concentrations are theoretically achieved with clinical injection, it is thought that this probably does not indicate the actual exposure to cells in their biologic environment [42].

1.8 Steps of Administration

The following steps go along with the technique used in the video accompanying this chapter. There are multiple variations to this technique which are acceptable. Of note, many experts skip the subconjunctival injection of lidocaine described in step 4, and simply use a cotton swab pledgett soaked in tetracaine or proparacaine for anesthesia. In addition, 30-gauge needles are quite prone to clogging with the preserved formulation of triamcinolone; this can complicate the injection. The clogging of the needle can lead to the needle actually rocketing off the syringe prior to or during the injection process. Many experts advocate the use of 27-gauge needles for triamcinolone injection to decrease the likelihood of these complications. Of note, some formulations of preservative-free triamcinolone are more easily

able to make it through a 30-gauge needle. It seems that the preservative-free preparations may be cleared from the vitreous faster. The increased particle surface area is thought to account for this.

Acceptable sterile techniques vary as well. The crucial point is that the triamcinolone being injected and the needle remain sterile. It is important that the antiseptic, betadine, be used to prepare the injection site. This can be accomplished without sterile gloves and drapes. The use of topical antibiotics is less important and not essential, although in practice they are frequently used. Some argue that the eyelid speculum is unnecessary. Many do not wear the indirect headpiece for viewing while injecting. The needle tip is simply aimed towards the optic nerve head and the injection performed.

1. Place 2 drops of topical anesthetic in the eye to be treated.
2. Prep the eye to be treated with a prepackaged povidone-iodine swab \times 2.
3. Place a drop of 5% povidone-iodine in the cul-de-sac.
4. After scrubbing and donning sterile gloves, in a sterile fashion, draw up the subconjunctival injection of 2% lidocaine with epinephrine 0.5 cc (from a fresh vial daily) and the triamcinolone 0.2 ml from a freshly opened vial. A sterile cotton tip is soaked in tetracaine solution. A 30-gauge needle is placed on both the anesthetic syringe and the triamcinolone syringe, but the solution is not pushed through.
5. Place a sterile lid speculum between the eyelids.
6. Place the topical-anesthetic soaked cotton tip on the conjunctiva for approximately 1 minute, then inject the local anesthetic to balloon the conjunctiva, using the cotton tip to disperse the anesthetic.
7. Using a sterile caliper, measure 4 mm from the limbus (in a phakic eye) or 3 mm from the limbus in a pseudophakic or aphakic eye.
8. Push the triamcinolone through to the tip of the needle to 0.1 cc total, and using a sterile cotton tip to stabilize the eye, inject 0.1 cc of triamcinolone into the vitreous cavity while observing the needle tip. Remove the needle and place a sterile cotton tip over the needle entry site for several seconds.
9. Immediately place a drop of topical broad-spectrum antibiotic solution over the injection site.

10. Observe the retina for perfusion of the central retinal artery.
11. Clean the eye, especially irrigating profusely with sterile water to remove all povidone-iodine solution.
12. Check the intraocular pressure 30 minutes post procedure and discharge if at a safe level.

1.9 Uses

Given that uveitis is relatively rare compared to macular degeneration and retinal vascular causes of macular edema, much of the data we have regarding the use of intravitreal TA is from the retinal literature. Nonetheless, intravitreal TA has been used numerous times for treatment in uveitis as well.

1.9.1 Retinal Disease and Surgery

Common retinal uses for intravitreal TA include treatment of macular edema in various diseases (including diabetes, central retinal vein occlusion, branch retinal vein occlusion, juxtafoveal telangiectasia, retinitis pigmentosa), neovascular age-related macular degeneration, Coats' disease, proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy, neovascularization of the iris (rubeosis iridis), as a visual aid in vitrectomy surgery, and as an adjunct in cataract surgery. Detailed discussion of the use in these conditions is beyond the scope of this text.

1.9.2 Uveitis and Ocular Inflammation

By definition, uveitis involves ocular inflammation. Macular edema can be a complication of many forms of uveitis. Thus, it is not surprising that intravitreal TA can be of significant benefit as a local therapy for uveitis. Local therapy to control inflammation and treat macular edema could allow the patient to avoid or reduce systemic immunosuppression.

1.9.2.1 Cystoid Macular Edema

Cystoid macular edema (CME) is a significant cause of vision loss in patients with uveitis. Inflammatory

“pseudophakic” CME can also cause vision loss following cataract surgery. Dramatic improvement in uveitic CME can occur with intravitreal TA injection (Figs. 1.1 and 1.2). As with other causes of CME, eradication of uveitic CME can, but does not always, correlate with improved visual acuity.

Kok et al. studied the effect of intravitreal injection of 4 mg of TA in 65 eyes of 54 patients with uveitis-related CME. Mean follow-up time was 8 months, and the best visual acuity occurred at a mean of 4 weeks following injection. They reported that 83% had a detectable improvement in visual acuity, of which 51% had at least either two Snellen lines or three Early Treatment Diabetic Retinopathy Study (ETDRS) lines of improvement. One third of those that initially improved had subsequent worsening of their visual acuity that correlated with worsening of CME in all cases. Mean follow-up time

for this group was 12.1 months. Two thirds maintained visual improvement for the follow-up period, but the mean follow-up period for this group was shorter (mean 6.7 months, range 3–13 months). Visual acuity in eyes with CME for greater than 24 months improved least while those with CME less than or equal to 12 months improved most. The mean improvement in visual acuity was only statistically significant in patients less than or equal to 60 years of age [28].

Intravitreal TA may improve CME secondary to birdshot retinochoroidopathy, immune recovery uveitis, chronic idiopathic uveitis, panretinal photocoagulation, multifocal choroiditis, refractory pseudophakic CME, and for treatment of CME and simultaneous reduction of graft rejection in patients who have undergone penetrating keratoplasty [30, 43–47]. In addition, patients with known uveitis at high risk for developing CME fol-

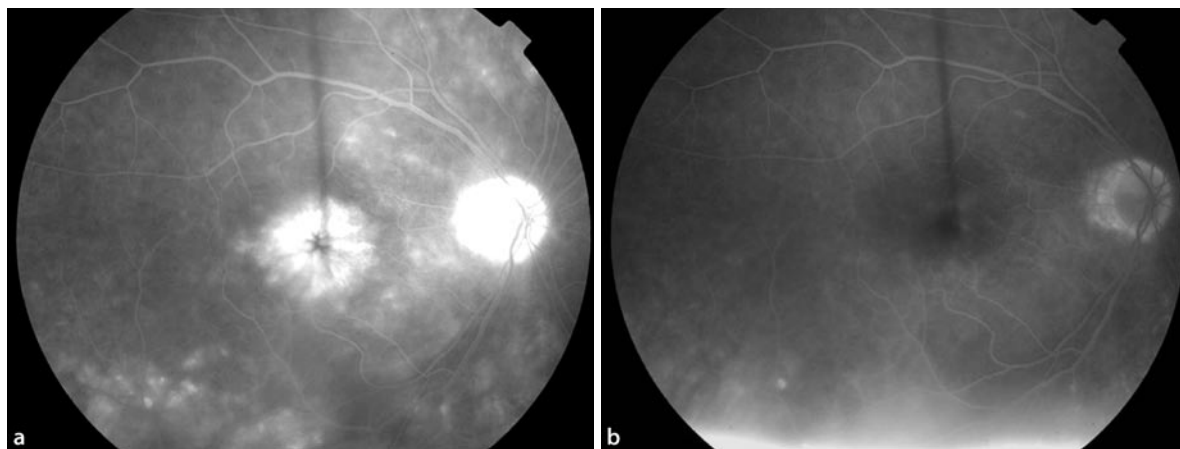


Fig. 1.1 A patient with a history of multifocal choroiditis, retinal vasculitis, and CME. **a** Late-phase fluorescein angiogram showing significant leakage consistent with CME. Visual acuity measured 20/70–1. **b** Late-phase fluorescein angiogram

of the same eye 3 months following treatment with 4 mg of TAAC by intravitreal injection. The leakage has improved significantly, but the visual acuity only improved to 20/60

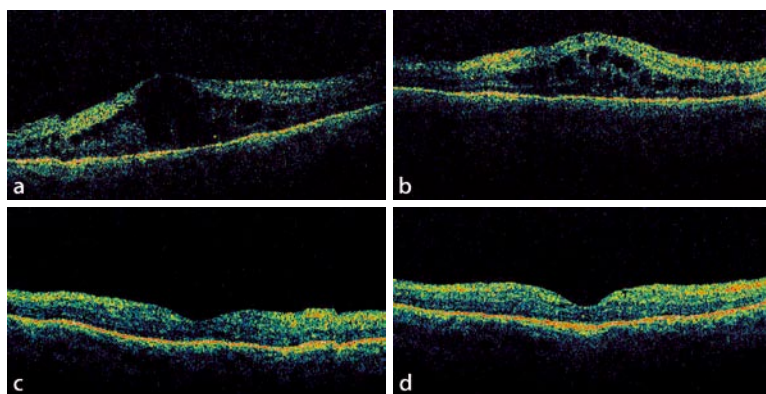


Fig. 1.2 OCT was used to document the response of CME in a 37-year-old female with bilateral panuveitis. She was treated with 4 mg of TAAC injected intravitreally. Baseline (**a**, **b**) OCT showing resolution of CME at 1 month (**c**) and 3 months (**d**) after injection. At baseline, visual acuity was counting fingers at 2 feet. At 1 month, it had improved to 20/200. At 3 months, postinjection visual acuity was recorded as 20/400+1

lowing cataract surgery can be given intravitreal or periocular TA at the time of cataract surgery to help prevent formation of CME and control inflammation. Patients with CME and pars planitis may benefit from intravitreal corticosteroid injection, although inflammation of the pars plana may complicate injection of the corticosteroid.

1.9.2.2 Sarcoidosis

Sarcoidosis is typically quite responsive to corticosteroid treatment. It is not surprising that intravitreal TA injection may have a role in some cases of sarcoid uveitis. Case reports have shown benefit in treatment of CME in patients with sarcoidosis [48]. In addition, regression of choroidal granuloma in sarcoidosis following three injections of TA at 2-month intervals has been reported [49].

1.9.2.3 Behçet's Disease

Reports have shown the benefit of intravitreal TA for treatment of CME and vitritis secondary to Behçet's disease. Duration of effect lasted 2–6 months [47, 50]. The TNF- α antagonist infliximab has proven to be very effective for the treatment of Behçet's. Since Behçet's is a systemic disease, it will frequently be preferable to treat systemically with infliximab, rather than locally with TA.

1.9.2.4 Eales Disease

Eales disease often presents with retinal periphlebitis and may progress to retinal ischemia, neovascularization, and vision loss. A case report has shown resolution of periphlebitis in a patient treated with intravitreal TA [51].

1.9.2.5 Vogt-Koyanagi-Harada Syndrome

Oral prednisone is the mainstay of treatment for Vogt-Koyanagi-Harada (VKH) Syndrome. Currently, it is generally well-accepted that long-term therapy (6–12 months) with oral prednisone following the diagnosis will reduce the risk of recurrence of inflammation. Commonly, high doses of oral prednisone are required in the acute phase, but clinical response will usually allow them to be tapered to lower doses within weeks. With this knowledge, it is not surprising that the serous detachments in the acute phase of VKH have responded to intravitreal TA injection [52]. However, since long-term

systemic prednisone therapy is generally recommended for this systemic disease, the additional risks posed by intravitreal injection in combination with its ability to only have a local effect, make it less desirable in cases of VKH. However, for patients who cannot tolerate the initial high doses of systemic corticosteroid that are often necessary, intravitreal injection may be a viable option. In the presence of serous retinal detachments, special precautions may need to be taken to avoid mechanical damage to the retina from the needle.

1.9.2.6 Sympathetic Ophthalmia

In contrast to VKH, inflammation in sympathetic ophthalmia is clinically localized to the ocular tissues. It is usually chronic, often requires long-term systemic immunosuppression, and may be difficult to control. Studies have shown short-term benefit of intravitreal TA injection in eyes with inflammation due to sympathetic ophthalmia. Long-term corticosteroid delivery devices may alleviate the need for repeat intraocular injection and may be a reasonable option in patients with sympathetic ophthalmia [53, 54]. Of course, the risk of devastating complications, such as endophthalmitis, must be given special consideration in patients who are functionally monocular.

1.9.2.7 Choroidal Neovascularization

Choroidal neovascularization (CNV) can be a complication of any disease in which there is a break in Bruch's membrane. In presumed ocular histoplasmosis syndrome (POHS), CNV can develop at sites of chorioretinal scars and, especially in the macula, can lead to significant vision loss. Oral and periocular corticosteroids have been reported to have a stabilizing effect on CNV due to POHS [55]. Intravitreal triamcinolone has also been reported to have a beneficial effect on CNV in POHS [56].

Other uveitic diseases such as multifocal choroiditis and serpiginous choroiditis can lead to development of CNV. Corticosteroids can be useful for inflammatory CNV, and use of intravitreal TA for treatment of CNV secondary to serpiginous choroiditis has been reported [57].

1.9.2.8 Toxoplasmic Retinochoroiditis

Use of intravitreal dexamethasone in combination with intravitreal clindamycin has shown some benefit in toxoplasmic retinochoroiditis. One study of four eyes in four patients showed a favorable response within

2 weeks after intravitreal injection of 1.0 mg/0.1 ml clindamycin and 1.0 mg/0.1 ml of dexamethasone. Two to four injections were required to achieve control of the retinochoroiditis. In addition, three of the patients continued on one systemic drug for treatment as well [58]. It should be emphasized that corticosteroid therapy, whether intraocular, periocular, or oral should not be initiated in toxoplasmic retinochoroiditis without sufficient antibiotic coverage. Corticosteroid therapy alone can promote recurrence or worsening of toxoplasmic retinochoroiditis. For similar reasons, longer acting depot steroids such as TA should be avoided as the corticosteroid effect may outlast the antibiotic effect, leading to unopposed steroid effect.

1.9.2.9 Hypotony

Chronic inflammation of the ciliary body can lead to decreased aqueous production, chronic hypotony, and hypotony maculopathy with visual loss. The IOP-raising side effect of intravitreal corticosteroid injection can be beneficial in these cases. In addition, reduction of ciliary body inflammation may also contribute to increased aqueous production, increased IOP, and resolution of hypotony maculopathy. Figure 1.3 shows the response to intravitreal TA injection as documented by OCT in a patient with hypotony maculopathy secondary to chronic uveitis associated with juvenile idiopathic arthritis (JIA).

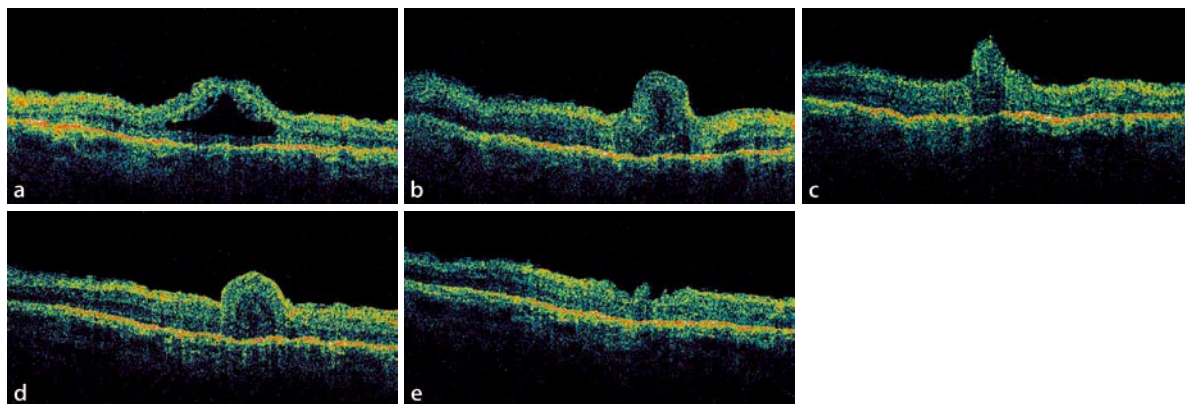


Fig. 1.3 Response as documented by OCT following injection of 4 mg of intravitreal TAAC in a patient with hypotony maculopathy secondary to chronic uveitis associated with JIA. **a** Baseline OCT showing hypotony maculopathy. Baseline visual acuity was 20/60. One week following the injection, the hypotony maculopathy had decreased, IOP was 4 mmHg, and visual acuity had decreased to 20/150. On biomicroscopy, the retina appeared to have folded upon itself, forming a cylindrical

1.9.2.10 Endophthalmitis

The role of systemic or intravitreal corticosteroids in the treatment of infectious endophthalmitis is a controversial topic. Some think that after adequate antimicrobial therapy is initiated, corticosteroid therapy can decrease inflammation and ocular tissue damage and therefore improve outcome. Studies in rabbits have shown that in conjunction with intravitreal vancomycin, intravitreal dexamethasone can decrease inflammation and tissue destruction. Studies in rabbits with *Streptococcus pneumoniae* endophthalmitis have shown that vancomycin is eliminated less readily from eyes which are concurrently treated with intravitreal dexamethasone. One hypothesis for this is that the corticosteroid decreases breakdown of the blood–ocular barrier, reducing this route of elimination. It is not known whether the dexamethasone alters the bactericidal activity of the vancomycin [59]. Further study is needed before any definitive conclusions can be drawn regarding the use of corticosteroids in the treatment of endophthalmitis.

1.10 Future

Intravitreal corticosteroid injections have become part of the therapeutic armamentarium of physicians who treat intraocular inflammatory diseases. Further advances are needed to limit the toxicity of intravitreal

cal cone with the apex at the fovea. **b** Line scan slightly nasal to the fovea where the retinal fold is broader. **c** Line scan through the fovea showing the apex of the cone where the retinal fold is sharper. By 2 weeks after injection, IOP increased to 6 mmHg, and the extent of retinal folding decreased. **d** Line scan nasal to the fovea at this time. **e** Line scan through the fovea at the same visit, documenting the decreased extent of folding at the fovea. Visual acuity improved to 20/60+1

therapy while maximizing the benefits. Injectable, longer-lasting steroid depots, such as the sustained-release dexamethasone implant (Posurdex™, Allergan) offer the potential of increased duration of action and have been postulated to have a lower likelihood of pressure elevation than standard intravitreal injection. The results of ongoing clinical trials in the treatment of anterior and intermediate uveitis may demonstrate whether these hypothesized benefits are significant. The implantable fluocinolone acetonide depot (Retisert™; Bausch and Lomb) is the subject of another chapter in this book. It is associated with significant benefit in some cases, although the rate of adverse effects such as cataract formation and glaucoma that requires trabeculectomy surgery is high. Other steroid delivery devices or molecules may someday provide different safety and toxicity profiles. Lastly, exploration in the use of other immunosuppressives, including the biologics, will surely be an area of interest in the future.

Take Home Pearls

- When performed by an experienced retina or uveitis specialist, intravitreal corticosteroid injection can be a safe and effective treatment for many conditions.
- Reports of benefit support the use of intravitreal corticosteroid for various types of uveitis that lead to CME, hypotony, inflammatory CNV, Behcet's Disease, VKH, and sympathetic ophthalmia.
- Numerous risks are present with injection. The most common are elevation of intraocular pressure, which may be transient or permanent, and cataract formation. The most severe is endophthalmitis.
- Intraocular delivery of medication has become more common in recent years. While other medications with fewer known side effects than corticosteroids may be preferred in some situations, intravitreal corticosteroid injection will likely play a role for years to come.

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Surgical Management of Inflammatory Eye Disease

Becker, M.D.; Davis, J. (Eds.)

2008, XIII, 267 p., Hardcover

ISBN: 978-3-540-33861-1