ABSTRACT

Steroids can intervene with many of the processes that lead to macular edema (ME). Steroids are potent anti-inflammatory agents, but they also have anti-vascular endothelial growth factor activity. Triamcinolone acetonide is probably the most commonly used steroid for ME, but it may not be the ideal formulation for ME. This article discusses several new steroid delivery systems: the fluocinolone acetonide implants and dexamethasone intravitreal implant. Drug-delivery systems under investigation have 2 fundamental approaches and philosophies: longer-acting reservoir implants with good long-term control of disease but with potential for drug or suppressive side effects, and shorter-acting, biodegradable inserts that potentially expose the eye to less drug or suppressive side effects but may not control disease as well. Sustained-release ocular implants lead to drug concentration gradients in eye tissues in which drug concentration is highest near the implant. Models of drug gradients based on implant location suggest that the implant can be shifted further into the eye, perhaps partitioning the drug better in the posterior segment and minimizing the anterior segment exposure.


MACULAR EDEMA (ME) results from a complex pathway of events, originating from vascular disease (diabetes or central/branch retinal vein occlusion) or as primary inflammatory disease (uveitis). ME due to vascular disease is strongly associated with vascular endothelial growth factor (VEGF) levels, whereas ME due to uveitis is due primarily to inflammatory mediators, such as interleukin-1 and tumor necrosis factor-α. Steroids can intervene with many of the processes in both pathways that lead to ME. Steroids are potent anti-inflammatory agents, but they also have anti-VEGF activity.

DIFFERENTIATING STEROIDS

Triamcinolone acetonide (TA) is probably the most commonly used steroid for ME, but is it the ideal formulation for ME? Corticosteroids are based on the cortisol structure, but they have several properties beyond chemical structure by which they can be distinguished, including anti-inflammatory potency, ability to translocate the glucocorticoid receptor complex to the nucleus, ability to transactivate or transrepress ligand-dependent gene sets and biologic responses, neuroprotection of the photoreceptors/retinal pigment epithelium, and direct cytotoxic effects.7

The Table shows the relative potencies of corticosteroids, and clearly TA is not the most potent.7 Although TA is used most consistently because of its formulation, drug-delivery systems are being developed that offer better choices for treating ME.

Another important way to distinguish among steroids is by their side effects. For example, in the Diabetes Clinical Research Network (DRCR) Protocol B study, 1- and 4-mg TA (Trivaris; Allergan, Inc, Irvine, CA; a micronized and lyophilized injectable suspension formulation) was compared to focal/grid
photocoagulation in patients with diabetic ME (DME). The results showed important side effects with TA: glaucoma and cataracts. Intraocular pressure (IOP) increased from baseline by 10 mm Hg or more at any visit in 4%, 16%, and 33% of eyes in the 3 treatment groups, respectively, and cataract surgery was performed in 13%, 23%, and 51% of eyes in the 3 treatment groups, respectively. Other steroids and steroid drug-delivery systems may show different incidences of cataract and glaucoma, which are the key ocular side effects associated with intraocular steroid use.

### Table. Relative Potencies of Corticosteroids

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Relative Potencies</th>
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<tr>
<td>Cortisone</td>
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<td>Cortisol</td>
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<tr>
<td>Prednisone</td>
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<tr>
<td>Triamcinolone</td>
<td>5</td>
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<td>Betamethasone</td>
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<tr>
<td>Dexamethasone</td>
<td>25</td>
</tr>
<tr>
<td>Fluocinolone acetonide</td>
<td>25</td>
</tr>
</tbody>
</table>


### Patient with Poor Visual Acuity and Diffuse DME in Both Eyes – Harry W. Flynn, Jr, MD

JO is a 43-year-old man with a 19-year history of non–insulin-dependent diabetes. He is pseudophakic in both eyes and had both focal/grid laser and pan-retinal photocoagulation in both eyes. Visual acuity is 20/200 OD and 20/400 OS.

Fundus photograph of the right eye reveals hard exudates in the center of the macula and a large circinate ring.

Optical coherence tomography (OCT) imaging (right eye) reveals diffuse retinal thickening (>500 µm), with slight vitreoretinal interface abnormality or cystic changes.

How would you treat his left eye? How would you treat his right eye? How would you manage this patient if your first-line therapy was not effective? For further discussion of the challenges in managing this real-life situation, please go to www.JHASIO.com/retinaldiseases.

### New Steroid Delivery Systems

Triamcinolone acetonide is discussed in more detail elsewhere in this monograph. This article discusses new drug-delivery systems under development, that are either US Food and Drug Administration (FDA) approved or pending approval.

#### Fluocinolone

The fluocinolone acetonide-containing sustained-release drug-delivery device (SR-DDD; Retisert; Bausch & Lomb, Rochester, NY) is surgically implanted through a 3.5-mm pars plana incision and delivers 0.59 mg of steroid total for up to 36 months. Fluocinolone is 25 times more potent than cortisol (Table), and its use in a chronic drug-delivery implant allows the usage of very low doses, which have been shown in clinical trials to be therapeutic. Currently, it is only FDA approved for uveitis. A phase III clinical trial in patients with DME is fully enrolled but approval has not yet been sought due to concerns about steroid-induced ocular side effects, particularly the high incidence of glaucoma, despite positive changes in visual acuity in some patients. After 3 years, 27.6% of patients who received the implant achieved at least 3 lines of improvement in visual acuity compared with 14.5% who received physician-determined standard of care (typically laser treatment). However, 18.9% and 15.9%, respectively, also lost at least 3 lines after 3 years of treatment. Safety data from the prescribing information show that eyes that receive the implant require significant monitoring. After 3 years, approximately 77% of those who received the implant required topical IOP-lowering drops, and 37% required filtering operations. The formation of cataracts after implant is also nearly ubiquitous in patients with DME (over 90% after 3 years, compared with 15% in the fellow eye). Cataract formation rises dramatically after approximately 18 months with the implant.

Another fluocinolone acetonide-containing implant, which is an injectable SR-DDD (Iluvien; Alimera Sciences, Inc, Alpharetta, Georgia), uses a non-bioerodible polyimide tube (3.5 mm long, 0.37 mm diameter) to deliver the corticosteroid (0.2 µg or 0.5 µg daily over 36 or 18 months, respectively). Both injectable fluocinolone SR-DDD implants studied in the clinical trial contain approximately 50% the amount of fluocinolone as the surgically implanted
SR-DDD. A 25-gauge inserter allows for a self-sealing wound, so the procedure can be done in multiple settings (ie, office, ambulatory surgery center, or hospital). The implant floats freely in the vitreous cavity, but tends to settle in the inferior vitreous base. The rationale for this product was to hopefully minimize ocular side effects such as cataract and glaucoma by further lowering the dose and to move the implant away from the eye wall and more into the inferior vitreous base.

The bioerodible fluocinolone implant has been studied in 956 patients with DME in 2 multicenter, international, randomized, double-masked, dose-finding, controlled trials (same protocol) comparing the 2 implant doses with standard of care (laser therapy). Although the data are not yet published, initial analyses of the pooled data show that 28.7% and 28.6% (low- and high-dose implant) gained at least 15 Early Treatment Diabetic Retinopathy Study letters at month 24, compared with 16.2% of those receiving standard of care ($P = .002$ for both treatment groups vs control). The differences with implant compared to standard of care were observed as early as month 1. Similarly, reduction in excess foveal thickness (measured by OCT) was seen by month 1 and remained dramatically different between low-dose implant and control throughout the study. The rates of IOP increase were much lower than with the surgically implanted fluocinolone SR-DDD, with 16.3% and 21.6% of the low- and high-dose groups having IOP greater than 30 mm Hg, compared with 2.7% in the control group. Additionally, rates of glaucoma surgery were much lower than with the surgically implanted fluocinolone SR-DDD, with 3.5% and 7.4% of the low- and high-dose groups, respectively, requiring 1 or more IOP-lowering surgeries, compared to 0.5% of the control group. However, cataract rates were very high—similar (though slightly lower) than what was found with the surgically implanted fluocinolone SR-DDD. Cataract was reported in month 24 in eyes that were phakic at baseline in 80% and 87% of the low- and high-dose groups, respectively, compared with 43.6% of the control group. Cataract surgery by month 24 in eyes that were phakic at baseline was required in 74.9%, 84%, and 23.1% of patients, respectively. Thus, cataract again will be nearly ubiquitous in patients who receive this implant, a risk that needs to be discussed with the patient. Glaucoma appears to be more manageable.

**DEXAMETHASONE**

A dexamethasone intravitreal implant (Ozurdex; Allergan, Inc, Irvine, CA) has been approved by the FDA for the treatment of ME caused by retinal vein occlusion. In this implant, the drug is embedded into a biodegradable polymer (polylactic glycolic acid). As the polymer degrades, the drug elutes over time and the remaining polymer subsequently breaks down to carbon dioxide and water. (By contrast, with the bioerodible injectable fluocinolone SR-DDD, there is a residual husk of polymer permanently left behind in the eye.) This implant was studied in 2 doses (350 and 700 µg) and was implanted using a 20-gauge incision in the phase II trial, though in phase III and in the approved product, it is injected into the eye through a 22-gauge injector. A phase II study in patients with ME caused by a variety of diseases (ie, diabetes, retinal vein occlusion, uveitis, and Irvine-Gass syndrome post cataract surgery) showed significant vision improvement through 180 days with the high dose (Figure 1).10 Patients with ME caused by uveitis or Irvine-Gass syndrome experienced particular benefit, but significant improvement in visual acuity was observed across all patient subtypes who received the 700-µg dexamethasone implant (Figure 2).10 Increased IOP was observed in some patients (17% and 12.9% in the 350- and 700-µg groups, respectively, compared with 0% in the observation group), as was vitreous hemorrhage (21%, 21.8%, and 0%, respectively), but cataract was not (15%, 17.8%, and 12.4%, respectively).10 (Please note: The phase III data leading to its approval are discussed in Dr Kuppermann’s second article.)

**EMERGING CONCEPTS IN VITREAL DRUG DELIVERY**

It is important to realize that sustained-release ocular implants may lead to drug concentration gradients in eye tissues, in which drug concentration is highest near the implant, for at least moderate periods of time. Models of drug gradients based on implant location show that, for example, a fluocinolone implant sutured to the eye wall has low but measurable aqueous levels (0.0008 µg/mL) and higher macular levels (0.0899 µg/g). By simply moving the implant by 4 mm, perhaps similar to the placement with the dexamethasone intravitreal implant or injectable fluocinolone SR-DDD, the aqueous levels of drug are no longer measurable and the macular levels of drug are...
4-fold greater (0.3602 μg/g). If there are drug gradients in vivo, we can take advantage of that and shift the implant further into the eye, and perhaps partition the drug better in the posterior segment and minimize the anterior segment exposure.

Also, the pharmacokinetics of freely injected intravitreal drugs are altered dramatically based on whether the eye is vitrectomized. However, pharmacokinetic studies of these emerging drug-delivery systems show no difference between vitrectomized and non-vitrectomized eyes in terms of retinal drug concentrations. Therefore, no longer does the vitreous act as a reservoir; rather, the implant is the reservoir.

CONCLUSIONS

Steroids are uniquely positioned to address the cascade of events leading to ME. Different steroids have varying potencies and toxicities. There are several ways to distinguish among the steroids used in ophthalmology, including chemical structure, anti-inflammatory potency, ability to translocate the glucocorticoid receptor complex to the nucleus, ability to transactivate or transrepress ligand-dependent gene sets and biologic responses, neuroprotection of the photoreceptors/retinal pigment epithelium, and direct cytotoxic effects. These differences may help to explain the differences among steroids in their safety and efficacy for the treatment of retinal disease.

Applying our current understanding of glucocorticoid pharmacology to drug discovery may lead to the development of ocular hypertension- and cataract-free steroids. Drug-delivery systems under investigation have 2 fundamental approaches and philosophies: longer-acting reservoir implants with good long-term control of disease but with potential for drug or suppressive side effects, and shorter-acting, biodegradable inserts that potentially expose the eye to less drug or suppressive side effects but may not control disease as well.

DISCUSSION

STEROIDS IN VITRECTOMIZED EYES

Dr Flynn: I often use steroids in vitrectomized eyes because steroid crystals have a longer effect in eyes with no formed vitreous compared to the rapid clearing with anti-VEGF agents. These crystals may adhere to the surface of the retina but there appears to be no toxic effect.
**Dr Kuppermann:** I also like to use TA post-vitrectomy, but because I am concerned about direct toxic effects of TA laying on the surface of the retina in vitreomized eyes, I prefer using a TA sub-Tenon’s injection at the end of the case for the same purpose and I found reasonable effects from that. Thus, there are still ways to use steroids and try to mitigate some of the potential for steroid toxicity.

**TA Formulations**

**Dr Flynn:** The standard injectable solution TA (Kenalog; Bristol-Myers Squibb, Princeton, NJ), which includes preservatives, was used mainly in 2004 and 2005. We became concerned about toxicity of preservatives, and shifted toward using preservative-free compounded pharmacy-formulated preparation, which became very popular. Another brand of TA (Trience; Alcon, Inc., Fort Worth, TX), which is an injectable suspension formulation, was more of a dispersive agent and was used often in surgery to help identify the vitreous. This product is popular among many surgeons. There is also the hydrogel-based injectable suspension formulation (Trivaris; Allergan, Inc, Irvine, CA), which was used in clinical trials such as DRCR and SCORE (Standard Care vs Corticosteroid for Retinal Vein Occlusion). The advantage of this formulation is that it forms a cohesive bolus of drug in the inferior formed vitreous and it is visible for months after the injection. Therefore we can choose from 3 different formulations of TA injectable. I think the retinal specialists generally have drifted away from the use of the standard TA injectable solution. I think it is relatively rarely used nowadays even though it is relatively inexpensive.

**Dr Nguyen:** Do you choose different steroids based on different types of patients?

**Dr Campochiario:** Until we get genetic data, there are some clinical features that we can use to tailor treatment. One is, of course, we tend to exclude any patient who has underlying glaucoma from the use of any steroids including steroid inserts. In addition, patients who have a family history of glaucoma may be more likely to have a steroid response. We do not know whether it is possible to identify patients by a stress test. We know that if a patient responds with increased IOP to topical steroids, that he or she is more likely after an implant to have increased IOP. So, certainly, if a patient has any history of a steroid response after topical steroids or any type of steroid administration, that would also make the patient less suitable as a candidate for steroid implant.

**Dr Davis:** The stress test idea is useful when it is positive, but changing any of 3 factors—dose, route of administration, and duration of exposure—might change a patient’s response. In the trials with the implantable device, patients were enrolled who had been exposed previously to regional corticosteroids and were not considered steroid responders, but some of them did have elevation of IOP from the device presumably related to the long duration of exposure with the device. Without genetic data, it is going to be difficult to know if someone is a responder, and even if they are genetically predisposed, dose, route, and exposure might still make a difference.

In a situation where you have perhaps no other equally effective therapy, is the increase in IOP necessarily a contraindication for use of the agent? We can assess on an individual basis the risks and benefits of remaining untreated with a potentially extremely useful agent versus potentially requiring glaucoma surgery. Central acuity can be lost forever from cystoid ME, whereas glaucoma surgery is generally considered manageable risk and a reasonably predictable surgery—not a perfect surgery but one that can be offered as part of the management of a patient.

**Dr Campochiario:** It is unlikely that genetic testing or stress testing will identify 100% of patients who are steroid responders, but it would still be useful to help rule out a certain percentage of patients understanding that such things are only tools and do not guarantee that a patient will not experience increased IOP from injection of a steroid insert. Certainly the duration of steroid exposure is very important in terms of developing glaucoma.

**Dr Kuppermann:** Most of us have migrated away from using the standard TA injectable solution because of the black box warning on the label and the fact that there is another formulation (TA injectable suspension [Alcon, Inc.]) that has an ocular indication.

**Dr Campochiario:** I still use TA injectable solution. I have not had many problems with it. It is certainly much less expensive, and it is more easily available than TA injectable suspension (Alcon, Inc). Has anybody seen any problems with this injectable suspension formulation when used for the treatment of ME? Several cases have been referred to me of patients who have had extreme dispersion of this formulation. It may not be as suitable as TA injectable solution, which tends to form a clump and get out of visual axes.
**Dr Kuppermann:** Most of us shifted away from TA injectable solution approximately 3 or 4 years ago because there was a cluster of cases of sterile endophthalmitis. Thus, I started using a compounding pharmacy preservative-free formulation of TA. With the TA injectable solution, it was always visible after 1 month, frequently visible after 2 months, and sometimes visible after 3 months. Once I switched over to the compounding pharmacy formulation, most of the time you do not see it at all after 1 month. TA injectable suspension (Alcon, Inc.) is somewhere in between, meaning it is usually visible at 1 month but it does not seem to have the visual visible durability of TA injectable solution. Candidly, I am thinking of shifting back to TA injectable solution as well, because I believe it has the longest duration in the eye of all the TA formulations.

**Dr Flynn:** TA injectable suspension (Alcon, Inc.) is always dispersive, especially in vitrectomized eyes. In anticipation of that event, I warn patients that for approximately 1 week, they will have a “snowstorm” with the drug dispersed in the vitreous cavity which definitely reduces their vision for a few days. This can even be significant when it disperses into a liquefied vitreous. TA injectable solution also can be dispersive but more often in large clumps.

**Dr Davis:** I no longer use TA injectable solution for intravitreal injection. With 2 FDA-approved products for ocular inflammatory disease, I see no reason to use it. The TA injectable suspension formulated by Allergan, Inc is not commercially available, but it has an FDA label for ocular use. The TA injectable suspension formulated by Alcon, Inc. is available. One situation in which I have used TA injectable solution is for vitreous visualization, because the crystal size is different from the injectable suspension formulation (Alcon, Inc). In some cases you get better visualization of the vitreous. Because it is rinsed from the eye at the end of the vitrectomy, I am less concerned about the toxic effects that might occur from the vehicle and preservatives.

**Dr Kuppermann:** Which is ironic because the primary label indication of that injectable suspension formulation is for visualization of the vitreous. You are saying TA injectable solution is better for that.

**Dr Do:** Right now, I still use TA for some cases of ME. However, like most ophthalmologists, I am concerned about the risk of elevated IOP associated with TA.

I will be curious to see if the decreased risk of elevated IOP with dexamethasone intravitreal implant holds up in the long term because the short-term studies have suggested there is less IOP elevation in dexamethasone-based SR-DDDs. Interestingly, in the injectable fluocinolone SR-DDD studies, there was not a bigger benefit with the higher dose than with the low dose, which was surprising because usually you see a greater reduction in retinal thickness or a greater improvement in visual acuity along with the higher dose of steroids. But the FAME (Fluocinolone Acetonide in DME) studies show that the dose and clinical response do not always correlate. In some steroid formulations, the lower dose may have better efficacy and decreased adverse events than the higher dose.

**Dr Kuppermann:** That is a very good point, particularly with the drug-delivery systems, because with chronic drug delivery you are saturating the receptors even with low doses. The ranibizumab intravitreal injection (Lucentis; Genentech, Inc, South San Francisco, CA) dosing is partially defined so that there will be some residual drug at 28 days at therapeutic levels. We are massively overtreating all our patients with intravitreal injections, in the sense that immediately after an intravitreal injection the dose is much higher than needed, but we are more concerned with extending the therapeutic window at the tail end of the treatment window. Once you saturate the glucocorticoid or VEGF receptors, you are already getting all the benefit you need out of that and you can minimize some of the collateral effects with the chronic low dosing of drug-delivery systems.

**Dr Schmidt-Erfurth:** We talk so much about different drug formulations that I think that we have forgotten that the real indication for steroid treatment is for inflammation. We have since learned that steroids may have some effect in other diseases such as vascular macular disease. But now that we have a whole spectrum of different types of drugs available, should we not use steroids for diseases that are inflammation-driven and try to find the best formulation with the longest durability and the lowest rate of side effects? And then for other diseases which are not primarily inflammatory, but for which we see that, for instance, anti-VEGF compounds have a good effect, try to find the lowest dose with the best efficacy and lowest side effects for those?

**Dr Campochiaro:** TA injectable suspension (Alcon, Inc.) is approved for use during surgery to
visualize the vitreous. That should not make us feel any better about injecting it for ME; it has not been studied for that. It is not proven to be any safer than TA injectable solution. This whole issue about preservatives being the cause of sterile endophthalmitis seems to be incorrect. It appears to be more a matter of the crystals because preservative-free TA does it, the TA injectable suspension formulation does it, anything that has particulate matter does it. The difference is that some patients just respond to particulate matter in their vitreous differently such that they get a bigger inflammatory response. Thus I do not think we should leave the impression that there is any particular steroid preparation that has been well studied for use in ME in terms of the free steroids and that there is no reason why TA injectable suspension is any better than TA injectable solution.

**Dr Kuppermann:** TA injectable suspension (Allergan, Inc) was studied in clinical trials. It is not commercially available, and because the hydrogel sequesters the crystals, it has not been associated with sterile endophthalmitis. But, because it is micronized, lyophilized, and has a small particle size, it may not have the durability and effect that we see with the TA injectable solution, which has the largest particle size of all the TA formulations.

**Dr Flynn:** I think there was an overreaction to blaming the preservatives in TA injectable solution. We now have large trials (DRCR Network Protocols B and I) showing similar low rates of endophthalmitis with intravitreal steroids, particularly in patients with diabetes, when you would expect higher rates. We know now that inflammation is part of the mechanism for diabetic retinopathy, which is not just a retinal vascular disease. Inflammation is important.

**Dr Kuppermann:** I am not sure that the separation of inflammatory diseases from VEGF-mediated diseases is quite true because we have seen that there is evidence that inflammation is part of all of these diseases, therefore there may be a partial blurring of the differences between the pathophysiology of the various retinal diseases of interest.

**REFERENCES**