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CME Activity

Intravitreal Corticosteroids: Ensuring Effective Use With IOP Control

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TARGET AUDIENCE

The target audience for this program is retina specialists.

LEARNING OBJECTIVES

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

- Identify risk factors associated with rises in IOP after steroid use
- Discuss management strategies for patients who experience rises in IOP after steroid use
- Assess clinical trial data pertaining to steroid implant therapies, including MEAD, FAME, BEVORDEX and OMAR

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Intravitreal Corticosteroids: Ensuring Effective Use With IOP Control

Safety concerns associated with corticosteroids are often cited as a reason why retina specialists may try to avoid using these agents in clinical practice. Certainly, various clinical trials looking at different agents in numerous disease states have demonstrated the potential for complications—the formation of cataracts and elevation in IOP being chief among them.

But just how concerned should retina specialists really be about the potential to induce complications? There is a well-known disconnect between the controlled environment of a clinical trial and clinical practice. Yet, even beyond the real world versus clinical trial paradigm, there may be important differences in the associated risks of a particular corticosteroid agent used and the route of its administration. Moreover, the indication for use may provide important context, vis-à-vis the importance and urgency of counteracting the inflammatory nature of the disease element being treated. It is well known that inflammation is a key component of both uveitis and diabetic macular edema. In every major clinical trial those patients who received delayed therapy never did as well as those who received prompt treatment.¹⁻³

In the following discussion, I am pleased to be joined by some leading experts in the field of retina medicine to discuss the complex and nuanced implications of IOP elevation after administration of corticosteroids. We will discuss the various options for using corticosteroids as well as highlight important data that can be used to inform clinical decision-making.

—Michael A. Singer, MD, moderator

STERIODS IN THE POSTOPERATIVE CARE OF PATIENTS

Michael A. Singer, MD: Let us start by discussing everyone's usage patterns for the various corticosteroid entities. How is everyone using steroids during the postoperative period?

Andrew A. Moshfeghi, MD, MBA: If a patient is coming to me from an outside clinic for a postoperative complication, such as a dropped nucleus or a cystoid macular edema (CME) following complicated cataract surgery, then more than likely he or she is already on a regimen of a nonsteroidal anti-inflammatory drug (NSAID) and steroid. I will usually switch that patient over to difluprednate or alter the frequency of the NSAID. When I perform vitrectomy surgery in my clinic as a primary indication, my usual steroid choice is prednisolone acetate 1% four times a day. If the surgery was for a macular hole or pucker, I will usually start the taper after the first week.

Maria H. Berrocal, MD: I do the same thing postoperatively: prednisolone acetate four times a day, and I also use a 4-week taper.

Gaurav K. Shah, MD: I do something similar, but I will also use more difluprednate twice a day until the bottle runs out if there is no past history of a steroid response. The reason I do that is that for some patients the copayment winds up being less expensive than using a generic. One of the great things in retina surgery is that the advent of 27-gauge instrumentation has made our surgeries less invasive, and so there is less of a need to keep patients on steroids past 4 to 6 weeks.

Tarek S. Hassan, MD: There are studies in cataract and postoperative vitrectomy patients that suggest that difluprednate has a higher likelihood of causing an elevated IOP response.⁴⁻⁶ However, using a topical medication is probably better than having nothing on board.

Dr. Singer: I think cost has become a factor, because both brand and generic prednisolone acetate 1% have gotten more expensive. Difluprednate is used more often during the postoperative period because of the lower copays. But what is the implication for pressure

elevations? Are physicians seeing a lot of pressure issues during the postoperative follow-up of patients?

Dr. Moshfeghi: In my routine cases, I rarely see pressure elevation, but for cases with more inflammation, including patients who need multiple trips to the OR or cases with proliferative diabetic retinopathy, I see pressure elevation in about 15% to 20% of cases.

Dr. Singer: And how do you treat it?

Dr. Moshfeghi: The first thing I do is withdraw the steroids appropriately, and that usually means hastening the taper or stopping it altogether. I will typically see the patient back within 7 to 10 days to make sure the inflammation is not going to be an issue. If the pressure is above 30, then I am going to treat without delay, and I will usually use brimonidine.

Dr. Berrocal: I normally do not see pressure elevations during the postoperative period because I taper very quickly. The one patient type where I do tend to see pressure issues is in patients with type 1 diabetes. In those patients I prefer to use prednisolone acetate 1% and to remove the steroid as soon as is appropriate. If I do encounter a pressure rise, brimonidine is my preferred option for treatment.

SUBCONJUNCTIVAL AND INTRAVITREAL CORTICOSTEROIDS

Dr. Singer: How is everyone using subconjunctival/sub-Tenon injections of corticosteroids?

Dr. Moshfeghi: I rarely perform a sub-Tenon injection, but when I do, it is typically for uveitis or cases where I feel a longer exposure to steroids is the most likely option for long-term control.

Dr. Berrocal: I use sub-Tenon injections a fair amount, especially for uveitis patients or in patients with CME that does not respond to a regimen of prednisolone acetate 1% and NSAIDs.

Dr. Hassan: I do not do many sub-Tenon injections, but when I do, it is in situations that Dr. Moshfeghi mentioned: refractory uveitis or uveitis with macular edema. On occasion, I use them intraoperatively toward the end of a vitrectomy for epiretinal membrane with significant CME, or a diabetic eye with a lot of edema. I am much more likely to use an intravitreal injection in situations where I think the patient needs a high intraocular load of steroids.

Dr. Singer: From a route of administration standpoint, it sounds as though sub-Tenon has become the exception more than the norm, and when they are used, it is typically for uveitis or refractory CME. What about intravitreal injection? How has your choice of agent evolved over time?

Dr. Moshfeghi: Early in my practice, I used Kenalog (triamcinolone acetonide; Bristol-Myers Squibb) and did not have many problems with it. Then Bascom Palmer Eye Institute, where

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—Andrew A. Moshfeghi, MD, MBA

I was practicing at the time, switched over to preservative-free triamcinolone, and later Triesence (intravitreal triamcinolone; Alcon), which is still what I use today.

Dr. Singer: Does anyone else have experience with preservative-free triamcinolone?

Dr. Hassan: It has been my experience that pseudo hypopyon is a frequent problem with regular intravitreal Kenalog, but I have never seen it with intraocular Triesence. In terms of efficacy, I do not know that there is a difference between the two.

Dr. Berrocal: I use mostly generic triamcinolone because of cost issues and insurance coverage among my patients. Many insurances in Puerto Rico do not cover Triesence. There are situations, such as in a monocular patient, where particles in the suspension will interfere with the remaining vision of an eye after vitrectomy. A dexamethasone intravitreal implant becomes a much better option because the half-life of triamcinolone is reduced in vitrectomized eyes,⁷⁻⁹ and the particles can impair vision in monocular patients.

Dr. Shah: In my practice, use of intravitreal triamcinolone has dwindled to the point where it is rare that we use it in the office. We use Triesence in patients who have had a prior issue with triamcinolone, but we prefer to use the dexamethasone implant when a steroid is called for in patients treated in the office.

Dr. Singer: The published literature suggests a rate of pressure elevation associated with intravitreal triamcinolone somewhere between 30% and 40%.¹⁰⁻¹³ However, Karl Csaky, MD, and others have shown that the particle size and distribution in the needle can vary quite significantly based on how vigorously the vial is shaken.¹⁴⁻¹⁷ Most people like to use a 4-mg dose, but based on that study, we can expect a lot of variance in the actual dose delivered. For the purposes of the discussion here, how confident are you in that 30% to 40% range? Does that align with your experience and is there any other context to consider?

Dr. Shah: We can certainly debate the validity of the 30% to 40% range, and it may well be much higher or lower. I think what is important to focus on is that about 3% to 8% of patients have an elevation to the 40 to 50 mm Hg range,¹⁰ which is a bigger issue. The rate of response is not as important as the magnitude of response I am seeing in a given patient. Generally, a patient with an IOP of 31 mm Hg after an injection of triamcinolone is something that I can manage medically. When the IOP starts to get higher than that, a more aggressive approach is needed.

JUDGING STEROID RESPONSE

Dr. Singer: How does everyone define ocular hypertension? Do you use a benchmark number in making a determination if a patient is at higher risk of developing pressure-related issues? Are there other factors you consider important?

Dr. Moshfeghi: Instead of using a particular pressure reading as an index of risk, I look at the whole context of the patient, especially if there is a difference between the two eyes.

Dr. Berrocal: I start to become concerned when the pressure rises over 23 mm Hg, but the difference between the two eyes is very important. I also consider the cup-to-disc ratio in building the risk profile.

Dr. Hassan: There is always a margin of error on IOP testing of around 2 to 3 mm Hg, so basing treatment decisions on an absolute number is potentially problematic. That said, when I get readings of 25 mm Hg, I start to be concerned. But as we talk about benchmark numbers, we also should remember that having ocular hypertension is different than being a glaucoma suspect, which is entirely different than actually having glaucoma. There are a lot of factors to consider, such as disc cupping, asymmetry of cup-to-disc ratio between the eyes, racial and demographic factors, just to name a few.

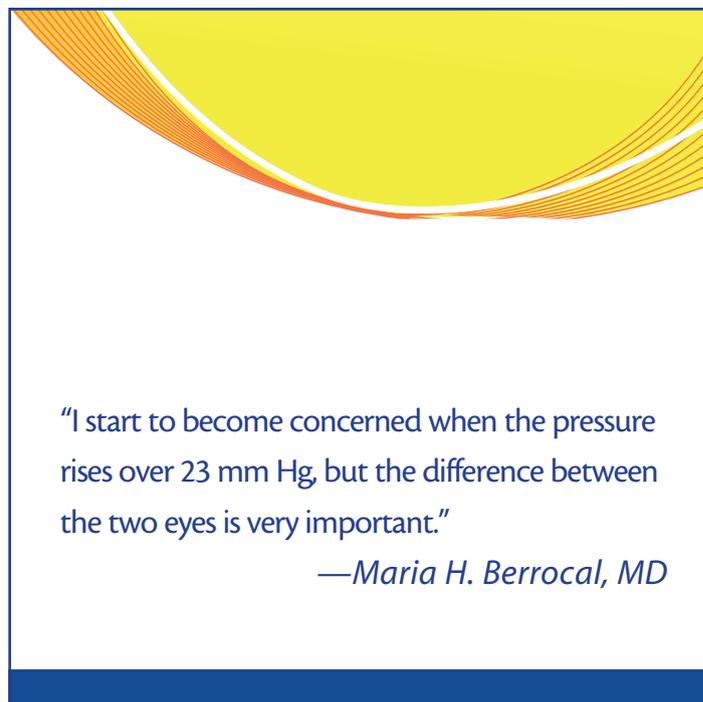
Dr. Shah: I agree, there are many variables to consider, but we also use 25 mm Hg as a benchmark at which we start to be concerned.

Dr. Singer: Does anyone perform pachymetry during the workup of patients with suspect pressure?

Dr. Hassan: Although we have the capability of doing pachymetry, we do not do it on a routine basis.

Dr. Berrocal: We do pachymetry on some patients with high myopia or if other questionable findings are noted. But it is not something we do routinely.

Dr. Moshfeghi: I believe the cases where we start to get high pressure readings are opportunities to share the care of the patient, and that may be a situation that is in the best interest of everyone involved. We certainly have the capacity to take pachymetry readings and to get peripapillary retinal nerve fiber layer readings, but what does that accomplish for our purposes? As a retina specialist, I question the value of that information,



because my objective is to treat retinal pathology. Pachymetry and retinal nerve fiber layer readings are not worthless, but how am I going to use them in the treatment of a diabetic macular edema (DME) or a retinal vein occlusion?

Dr. Hassan: If you practice in an area where there is limited access to care, there may be rationale for the retina specialist to do more. However, where I am, in the metro Detroit area, there are several opportunities to comanage such patients with another eye specialist. I think that often gives patients great comfort because they are sophisticated enough to know that the retina specialist is worried about something other than the intricacies of elevated eye pressures.

Dr. Singer: In my clinic, I start to become concerned when I see pressure readings of 23 mm Hg. I use pachymetry if the number is high so that I can get a better understanding of what is going on in the eye in terms of corrected IOP.

In terms of response rates, what can we expect from the individual agents?

Dr. Moshfeghi: I do not have personal experience with the fluocinolone acetonide 0.19 mg implant, but the published literature provides a starting point to understand what may be expected in clinical practice. In the FAME study, 3.2% of patients in the low-dose group had a pressure elevation and incisional glaucoma surgery was required in 3.7% of patients in the low-dose group compared with 0.5% in the sham group; the rate of laser trabeculoplasty was also higher in the low-dose group compared with sham (0.8% vs zero).¹⁸ The next would be intravitreal triamcinolone, followed by the dexamethasone intravitreal implant. In the MEAD study, 42% of patients required an IOP-lowering agent per protocol and 1.2% required a surgical intervention for elevated IOP.¹⁹

Case Discussion

Dr. Singer: Let us talk about a few hypothetical scenarios. Mrs. Jones has been administered a corticosteroid. Upon follow-up, her IOP reading is 28 mm Hg. Is anyone concerned enough to start therapy?

Dr. Moshfeghi: If the pressure is 28 mm Hg, I might start therapy with a single agent, depending on if there are other factors that give me pause. I would want to know the baseline IOP, for instance, and what degree of rise I am seeing. That said, I would probably opt for brimonidine versus a combination agent like brimonidine tartrate 0.2%/timolol maleate 0.5% or dorzolamide hydrochloride 2%/timolol maleate 0.5%, which I am more likely to use if the pressure is in the 30s.

Dr. Singer: And when do you see the patient back?

Dr. Moshfeghi: I would bring the patient back within 1 to 2 weeks.

Dr. Singer: Is a single agent usually successful in that scenario?

Dr. Moshfeghi: Usually, yes, it is.

Dr. Singer: Now let us say that the steroid was a dexamethasone implant. At the 6 to 8 week follow-up, the pressure is 28 mm Hg and an optical coherence tomography central field showed thickness less than 300 μ m. Anatomically there is a response, but is the pressure reading concerning?

Dr. Hassan: I would say, by and large, I am not going to give them another steroid unless there are mitigating circumstances. For example, if someone being treated for diabetic macular edema (DME) has difficulty getting to the clinic for frequent anti-VEGF injections or there are cost concerns, I might consider repeating the implant after a long conversation about the risks.

Dr. Singer: Does your thought process change if anti-VEGF injections are not effective? For the sake of the scenario, we are talking about a patient being treated for DME. Let us say that an attempt to extend the treatment interval has not been successful. What is your next step?

Dr. Moshfeghi: At that point, I would like to get the patient involved so I can present the various options. One option is to go back to an every 4-week injection protocol with anti-VEGF drugs but with the caveat that it may not be entirely effective. I am assuming that different anti-VEGF agents have been attempted and that the patient is on the most potent agent available for use. What I do not want to do is put the patient at risk for glaucomatous optic neuropathy, which is why I would prefer an anti-VEGF agent. I prefer aflibercept, in particular, because that is the most potent anti-VEGF drug we can use for DME.¹ If the patient still does not want to go that route, I will discuss the potential to induce pressure responses.

Dr. Berrocal: That is an interesting problem. If the patient responded to the dexamethasone implant, did not respond to anti-VEGF therapy, but the pressure is elevated, I would consider using dorzolamide hydrochloride 2%/timolol maleate 0.5% and continuing to use the implant. I may increase my vigilance in observing this patient or get a glaucoma specialist involved for an extra layer of security.

I actually had a patient like this recently, who only responded to the dexamethasone implant but had developed glaucoma after triamcinolone that required filtering surgery. I tried to change to anti-VEGF injections, but there was no response. Therefore, we went back to using the dexamethasone implant because that was the only thing that provided therapeutic benefit.

Dr. Singer: Were there any optic nerve changes?

Dr. Berrocal: Yes, prior to the filtering surgery.

Dr. Singer: Has that patient lost any significant visual field?

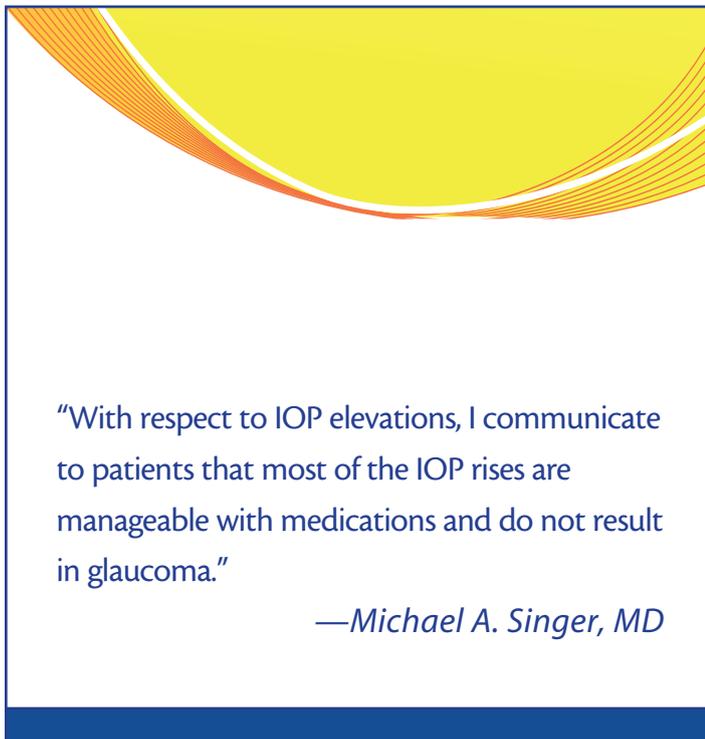
Dr. Berrocal: No, he has not. The filtering procedure has kept his pressures low despite the dexamethasone implant.

Dr. Singer: We have been discussing a scenario in which the pressure was 28 mm Hg. Does your thinking change if the pressure is 38 mm Hg?

Dr. Hassan: It is a different scenario with a pressure of 38 mm Hg. It is important to remember that there is not a cumulative risk of pressure elevation following multiple injections of the dexamethasone implant. So if the pressure response after the first time is 28 mm Hg it is extremely unlikely there will be more of a response after repeat use. At 28 mm Hg, I will use the implant, but at 38 mm Hg, I am a little hesitant. Another thing I can consider in this situation is to alternate between anti-VEGF agents and the dexamethasone implant in subsequent treatments.

Dr. Shah: I agree. If the steroid is the only thing that is helping the patient, I would not be afraid to use steroids in somebody with glaucoma. Another factor in all of this is that the treatment options for glaucoma have really expanded, including the advent of ab interno minimally invasive procedures. The topical therapies are better than ever, the laser options are superior to what was used in the past, and surgery, should it be necessary, does not necessarily have to be an invasive incisional procedure.

1. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-1203.



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—Michael A. Singer, MD

Dr. Berrocal: In my experience, pressure variation after the dexamethasone implant is predictable. If a pressure spike is going to occur, it will typically be at 6 to 8 weeks,¹⁹ which works out conveniently for when I want to see the patient back in the office for a recheck. With the implant, as with all the steroids, there is a risk for cataract formation in phakic patients, and rates of conjunctival hemorrhage and vitreous detachment were higher in the clinical trials among patients in the implant group versus sham. Fluocinolone acetonide 0.19 mg implant and intravitreal triamcinolone both raise pressure in a much less predictable fashion, and, hence, I have to monitor those patients much more closely.

Dr. Singer: Whenever possible, I try to use sustained-release steroids. Among phakic patients, if I am using either the dexamethasone or fluocinolone implant, I will convey that there is a very good chance that they will get cataracts over time, but cataracts are treatable, and, with multifocal lenses, that there is a good chance that they will not be dependent on glasses for distance or reading. With respect to IOP elevations, I communicate to patients that most of the IOP rises are manageable with medications and do not result in glaucoma.

Dr. Hassan: In my practice, the dexamethasone implant is the most predictable steroid I use. Pressure issues are very rare in my patients, which reinforces what we saw in the clinical trials. The topical agents have some potential to elevate pressure. There are actually scenarios, such as in a patient with low pressure, where you use them because you want to induce a slightly elevated pressure response. I find that intravitreal triamcinolone, on the other hand, is unpredictable, and you have to watch patients closely, especially as you repeat injections over time. With the dexamethasone implant, there does not seem to be an additive risk with repeat use.

Dr. Singer: In terms of IOP elevations, there is much more understanding of the IOP response after a dexamethasone versus a fluocinolone implant. There was a subset analysis presented at the American Society of Retina Specialists annual meeting 2 years ago that was later published showing the chance of getting an IOP spike greater than 10 mm after the first time a dexamethasone implant is used is about 25%. Then after the second time it is used, the risk is about 15%. For three or more, it is under 10% risk that a pressure elevation will occur.²⁰ That is definitely not the case for triamcinolone.

In terms of the fluocinolone implant, there is not a lot of evidence to help predict who will get an IOP response. In the FAME study, 34% of patients had an IOP of greater than 10 mm Hg and 20% of had an IOP over 30.¹⁸ However, this was of the entire population. The current label recommends that patients undergo a steroid challenge prior to the use of fluocinolone implant, so these numbers probably will be lower in regular clinical practice. We do not have data yet to support this; however, PALADIN²¹ is a phase 4 study of the fluocinolone implant designed to look for safety signals. Data from this trial should help us better understand the IOP issue in patients treated with the implant.

Dr. Singer: Based on what we just talked about, when does everyone like to bring the patient back for an IOP check after administering the various kinds of steroids? Does it differ based on the agent?

Dr. Moshfeghi: If I have used the dexamethasone implant, then checking for a pressure elevation at around 6 weeks should be sufficient. That is usually when I am bringing the patient back for a follow-up appointment anyway.

Dr. Shah: There are some patients who get a late pressure rise after triamcinolone, sometimes as late as 3 to 4 months later.

Dr. Singer: That is a good point. Should that change when a patient is seen back for a pressure check?

Dr. Hassan: I think it depends on what is being treated and when you expect to see a response to their underlying condition.

DISCUSSING RISKS OF STEROIDS WITH PATIENTS

Dr. Singer: One of the recommendations around the fluocinolone acetonide 0.19 mg implant is to do a provocative steroid test before using it. What steroid would you use for that provocative test?

Dr. Hassan: I think I would probably use a triamcinolone injection because I want to see if they really do have this issue specifically with the steroids. The dexamethasone implant is such a well-controlled delivery system that I am not sure it would be useful for this purpose. What does not really make sense to me is to use a topical agent, because of the significantly lower concentration of steroid delivered to the eye compared to an intravitreal injection.

Dr. Singer: What risk factors do you consider potentially important as suggesting a risk for steroid response?

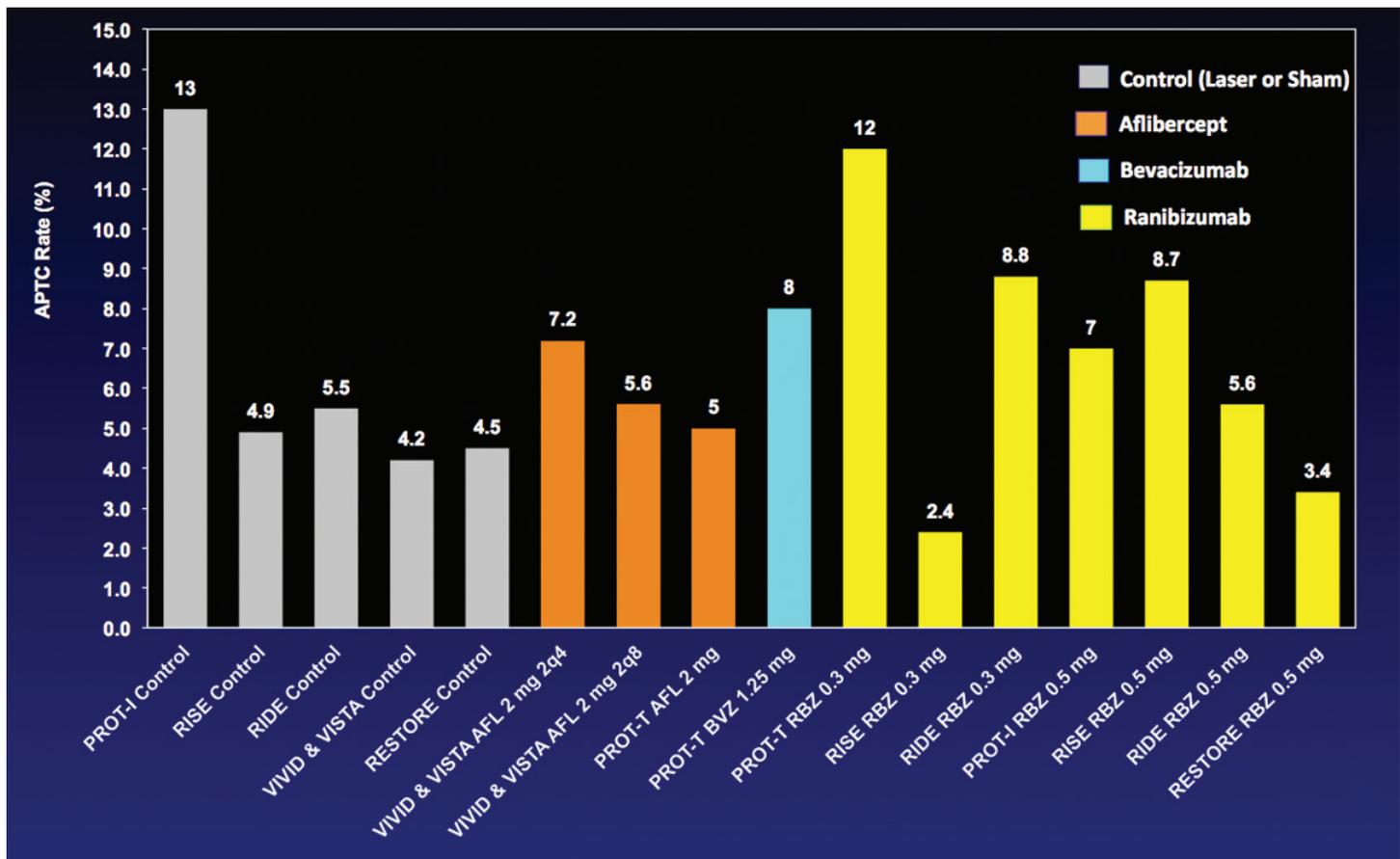


Figure. Two-year APTC event rates across DME studies of anti-VEGF agents.

Dr. Berrocal: Steroid response is not typically predictable, but some risk factors I note are myopia,²² diabetes,^{23,24} and family history of glaucoma.²⁵⁻²⁷ A number of factors have also been identified in the literature, including previous IOP response,²⁸ very young or old age,^{29,30} connective tissue disease,^{31,32} and previous penetrating keratoplasty.³³

Dr. Singer: Is glaucoma a contraindication for giving a repeat intravitreal injection?

Dr. Hassan: The severity of the glaucoma is a factor for me. If it is a patient who is well controlled on one glaucoma drop, I am less concerned than if it is a patient who is moderately controlled or uncontrolled on two drops, in which case it would have to be severe macular edema for me to inject an intravitreal steroid.

Dr. Singer: What do you discuss with patients about the risks of using an anti-VEGF agent?

Dr. Hassan: The main thing I discuss is the possibility of infection. I, of course, also talk about the possibility of a lack of response. Those are the two main things I think are important to relate to the patient.

Dr. Singer: Do you mention stroke risk?

Dr. Hassan: I do not, generally, unless the patient has had a recent history of a stroke.

Dr. Singer: What about everyone else?

Dr. Berrocal: No.

Dr. Shah: I do not.

Dr. Singer: And what is your thinking with regard to stroke events?

Dr. Hassan: We have not seen definitive data showing a link between using anti-VEGF drugs and a higher risk of APTC events. There have been signals in the various studies, but so far, the weight of the evidence to declare a true cause and effect is just not there.

Dr. Singer: If we look at the various anti-VEGF trials, the average rate of APTC events after 2 years was about 5% to 7% (Figure). When we look at risk of needing glaucoma surgery after a steroid injection in the major clinical trials, it was about 5% in the FAME study,¹⁸ about 1% with the dexamethasone implant,¹⁹ and about 1% in the Jonas study looking at intravitreal triamcinolone.¹⁰ Looking at these two issues, the rates of incisional surgery after steroid use and rates of APTC events after anti-VEGF are similar. I think most people would agree that it is prudent to discuss glaucoma risks with

steroids, yet most people do not talk about stroke risk with anti-VEGF drugs. Are we being cavalier about the risk of stroke or should we be rethinking the kinds of discussions we have with patients about risks?

Dr. Shah: I am not sure these are necessarily comparable. As Dr. Hassan alluded to, we do not definitively know if APTC events are related to anti-VEGF drugs, whereas IOP rise after steroid use is something we talk about because we know it is a potential risk.

Dr. Hassan: I think we need to consider the believability of the risk. We absolutely know that using steroids can, in some instances, lead to glaucoma, and a certain percentage of those that get glaucoma will need surgery to gain control. However, with APTC events, there is not good evidence that a patient's risk is elevated by exposure to an anti-VEGF, but we do know that fewer than 1% of patients will develop endophthalmitis. There is a real, albeit very small, risk of infection following anti-VEGF injections, but an unknown and likely unrelated risk of APTC events.³⁴⁻³⁸

I think we also need to think about the alternatives in this context. If we are concerned about glaucoma with steroids, we likely have another treatment option. With anti-VEGF drugs used as primary therapy, there are very good data in several disease states that demonstrate why it is preferred therapy for its various indications. Often, there is not a second comparable option to anti-VEGF drugs.

Dr. Shah: I may mention this signal to patients receiving an anti-VEGF who have a recent stroke history, but it has been my experience with those kinds of patients that they still want the anti-VEGF for their chief complaint. Even if they are on an anticoagulant for a very serious systemic issue, these patients are very concerned about losing vision.

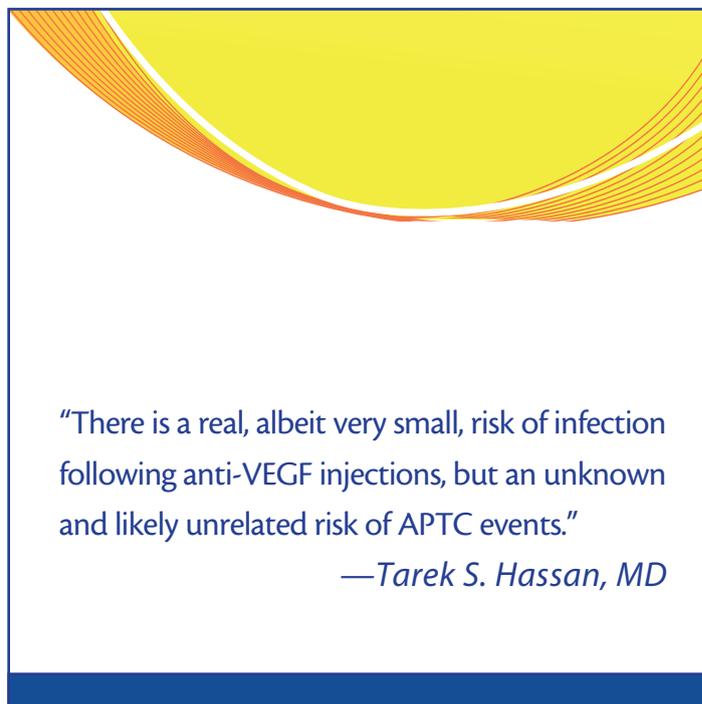
Dr. Berrocal: If you are comparing risks, you can also look at the control groups of these respective trials. In the case of glaucoma risk in patients administered steroids, there is almost no pressure elevation in the control groups in the major clinical trials. But with APTC events, they occur in almost equal frequency in active and control arms of studies involving anti-VEGF drugs.

Dr. Moshfeghi: I occasionally have a patient who brings this issue up. When that happens, I let him or her know there is a theoretical risk associated with the class of medications, but that the data have not shown a statistically significant risk.

COMBINING THERAPIES

Dr. Singer: While there are not evidence-based treatment guidelines for the concomitant use of anti-VEGF agents and steroids, a lot of retina specialists use this approach in the treatment of DME. Does anyone use combinations of therapies in the clinic?

Dr. Moshfeghi: I do, and it is mostly because the treatment algorithm in DME is not really a clear-cut progression from one agent to the next. I am usually not switching agents from anti-VEGFs to steroids; more typically, I am adding to the anti-VEGF regimen in some



“There is a real, albeit very small, risk of infection following anti-VEGF injections, but an unknown and likely unrelated risk of APTC events.”

—Tarek S. Hassan, MD

fashion, even if the patient is not responding to the intravitreal injections the way I would like. I may add a dexamethasone implant but that does not necessarily mean I am subtracting the anti-VEGF.

Dr. Berrocal: I do something similar. If I am getting a suboptimal response to an anti-VEGF drug, I will add a dexamethasone implant to see if there is a benefit. If there is a marginal response, I am less inclined to stop the anti-VEGF. But if there is a really robust response, I may suspend the anti-VEGF to decrease the burden of treatment.

Dr. Singer: If you are using both anti-VEGF agents and a dexamethasone implant, when do you retime the reinjection of the implant?

Dr. Moshfeghi: That is a difficult question because if I am incorporating a dexamethasone implant, it is usually in an eye that is not doing well, and so the treatment goal is not to extend the duration of action. Speaking generally, I would expect to reuse the implant on almost the same timing frequency as if an anti-VEGF agent were not being used. In other words, I would reuse it about every 4 months.

Dr. Berrocal: I would say it depends on the patient, because the response can be variable. Some patients need a reinjection of the dexamethasone implant every 3 months while others may be able to make it to 4 months before they require a reinjection. When using anti-VEGFs, I like to see the patient 4 weeks after the injection to check for response to the drug. If there is a response, then I continue the anti-VEGF but add the dexamethasone implant if edema persists.

Dr. Shah: I am cautious about telling a patient that he or she failed therapy. I do not use that word because I use sequential therapy and I may start a patient on anti-VEGF injections, switch to

steroids, but then go back to the anti-VEGFs. Different therapies may be appropriate at different stages of the disease.

Dr. Hassan: My approach is probably somewhere between sequential and concomitant, exactly for the reason being highlighted by the rest of the panel: the response to therapy is patient specific. DME is a disease caused by multiple mechanisms, and every person has a different mechanism that is the primary driver. The mechanism may even evolve and change over the course of the patient's disease based on how well the overall disease state is controlled. For that reason, having a fixed regimen is limiting and not in patients' best interest. I agree with the concept of gauging the patient's response to therapy. If a dexamethasone implant completely dries a patient out who had fluid on the retina despite anti-VEGF injections, then there may be rationale to use the implant as monotherapy for a little while. For the majority of people, a dexamethasone implant will yield a significant reduction in fluid, but they still may need an anti-VEGF to get the retina completely dry.

I think you also need to weigh the potential for disease modulation in response to treatment. Anti-VEGF drugs have an impact on the underlying diabetic retinopathy,^{39,40} but we also know that diabetic retinopathy is reduced by long-term steroid use. Whether there is a quantifiable difference between steroids and anti-VEGF drugs in terms of diabetic retinopathy management is unknown and its likely highly variable. Therefore, I think it is prudent to judge the need for retreatment based on how the patient is responding on a number of different parameters to the chosen treatment approach.

Dr. Singer: Most of the combination therapies that I perform are dexamethasone implant and anti-VEGF agents, although I have used combination therapy with some patients using the fluocinolone implant. When I rechallenged these fluocinolone patients with anti-VEGF agents after the appearance of rebound edema, I found that the effect of the anti-VEGF agent lasted at least 4 months, much longer than I expected. I believe this is due to the fact that the pharmacokinetics of the implant allows it to release a very low dose of steroid over a very long period of time. It may also be that the rebound edema is a VEGF-mediated process, and, therefore, the inflammatory component is still being controlled by the implant but the VEGF component is breaking through. I would look forward to future studies that investigate these possibilities.

CONCLUSION

Dr. Singer: One of the key things we have talked about is the need to individualize the approach to treating patients. It is important to remember that although therapy is approved based on clinical trials, implementation may vary in clinical practice. What I think came out of our discussion is that individualization of therapy continues through the follow-up of patients, and this is actually a very logical extension of the principle. For, if we are going to be mindful to select the therapeutic approach most likely to achieve success based on any number of factors, we should be diligent about adjusting the strategy based on the response. If we would add and subtract additional interventions based on efficacy, we should also do so based on safety.

When it comes to the administration of corticosteroids, the panel has highlighted some important differences in the various formulations of steroids available for clinical use; the overall suggestion is that the risk of elevated IOP differs by route of administration, and that not all corticosteroids are equal in safety and efficacy. It is also important to keep in mind that IOP elevation is not homogenous; in fact, IOP response to corticosteroids is variable and patient specific, and, therefore, we owe it to patients to closely monitor for any potential change in pressure that, if untreated, may possibly lead to glaucomatous optic neuropathy. However, in spite of this, it is important not to discount the efficacy of corticosteroids based on their potential side effect profile, because any increase in IOP is usually easily managed by topical medications. ■

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INTRAVITREAL CORTICOSTEROIDS: ENSURING EFFECTIVE USE WITH IOP CONTROL CME QUESTIONS

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- According to published studies, which of the following is most correct with regard to delayed initiation of treatment among patients with macular edema secondary to retinal vein occlusion (RVO), diabetic macular edema (DME), or uveitis?**
 - Delayed treatment of macular edema has no bearing on visual outcomes in RVO, DME, and uveitis; patients in most trials achieved similar visual outcomes with delayed treatment as they did with prompt treatment
 - Delayed treatment of macular edema may result in incomplete resolution of the anatomy in RVO, DME, and uveitis, but no link to visual outcomes has been identified
 - Results from major clinical trials of individuals with RVO, DME, and uveitis indicate that delayed treatment of macular edema may result in incomplete visual gain compared with prompt initiation of treatment
 - Delaying treatment of macular edema may be most consequential with respect to visual outcomes among patients with uveitis, although patients with RVO or DME can likely be followed for long periods off treatment without harming the potential to gain vision
- Approximately what percentage of patients administered an intravitreal injection of triamcinolone will experience an elevation in IOP?**
 - 10% to 20%
 - 20% to 30%
 - 30% to 40%
 - Greater than 50%
- Among individuals who do exhibit elevated IOP secondary to exposure to intravitreal triamcinolone, approximately what percentage experience elevation into the 40 to 50 mm Hg range?**
 - Between 3% and 8%
 - About 10%
 - About 15%
 - About 20%
- Use of combination therapy involving a steroid implant and anti-VEGF agents for treatment of macular edema is supported more so by anecdotal evidence than by clinical trial data.**
 - True
 - False
- When discussing the safety profile of steroids and anti-VEGF agents, the panel concluded that relaying the potential for IOP elevations after steroids was prudent, but that it may not be necessary to discuss possible APTC events following anti-VEGF injection. What was the stated reason?**
 - There is a definite risk of IOP spike after administration of steroids but no such causal link has been established with APTC events following anti-VEGF injections
 - There have been more studies looking at the issue of IOP spikes following steroids than studies looking at APTC events after anti-VEGF injections
 - The issue of APTC events following anti-VEGF injections has not been studied
 - There is not a recommendation from a recognized professional organization suggesting a need to discuss APTC events following anti-VEGF injections
- The half-life of an intravitreal injection of triamcinolone is about the same in an eye after a vitrectomy compared with an eye that has not undergone a vitrectomy.**
 - True
 - False
- What was the rate of incisional surgeries required to treat glaucoma in the phase 3 FAME (flucinolone acetonide 0.19 mg implant) and MEAD (dexamethasone intravitreal implant) trials?**
 - Zero in both studies
 - 3.2% in the low-dose group FAME; <1% in MEAD
 - Zero in either treatment group in FAME; 5% in MEAD
 - 5% in both studies
- History of glaucoma is an absolute contraindication for continued use of a local corticosteroid, regardless of the retinal pathology being treated.**
 - True
 - False
- Based on the panel's discussion, which of the following is the most correct statement with regard to risk factors to predicting a steroid response?**
 - Myopia, diabetes status, and family history of glaucoma are useful, but previous history IOP response is not a relevant risk factor
 - Myopia, diabetes, family history of glaucoma, and previous IOP response are all relevant risk factors, and there are additional factors that may also be useful to identify
 - Myopia and family history of glaucoma are the most important, but diabetes status is not factor; other factors may or may not be relevant
 - Previous history of IOP response is strongly associated, and there are really not any other known risk factors
- What was the panel's consensus on the value of gathering pachymetry data in a patient who experiences an IOP elevation following exposure to a corticosteroid?**
 - It likely would provide additional information useful for managing the patient
 - While pachymetry data might be relevant for understanding the overall health of the eye, this data would be unlikely to affect how the retinal pathology is treated
 - It should be recorded and shared with the comanaging specialist
 - There is no role for pachymetry in the management of glaucoma

ACTIVITY EVALUATION

Did the program meet the following educational objectives?

Agree Neutral Disagree

Identify risk factors associated with rises in IOP after steroid use

Discuss management strategies for patients who experience a rise in IOP after steroid use

Assess clinical trial data pertaining to steroid implant therapies,
including MEAD, FAME, BEVORDEX and OMAR

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