Intravitreal triamcinolone acetonide has gradually worked its way into the realm of modern medical retina care despite having never withstood the rigors of a vigorous clinical trial. The drug, which has been around since the 1960s and carries a specific warning not to be used in the eye, has found increased use over the past several years for the treatment of macular edema from various etiologies. If surveys are to be believed, most of us are currently using this drug as a part of our therapeutic regime, although often not as a first-line treatment. Having been one the original individuals to use intravitreal triamcinolone for macular edema, I was asked to provide some background regarding the evolution of this concept.

BACKGROUND

Having trained as a resident at Indiana University under Ron Danis, MD, and Tom Ciulla, MD, I was exposed to the feasibility of injecting triamcinolone (Kenalog 40, Bristol-Myers Squibb) directly from the bottle into the vitreous cavity. They were studying this drug as a treatment for exudative age-related macular degeneration (AMD) in the era before verteporfin with photodynamic therapy (Visudyne with PDT, QLT/Novartis); at this time, antivascular endothelial growth factor (anti-VEGF) therapy was in its early clinical evolution.

I left residency before the completion of the study, so I did not have an opportunity to evaluate efficacy in any objective manner. However, I was convinced that this appeared to be a safe therapy barring any long-term unforeseen damage at the molecular level. Of course I was aware of the predictable potential adverse effects of intraocular pressure response and cataractogenesis with use of corticosteroid medication, as well as the intrinsic risks associated with any intraocular injection.

In 1999, I had the good fortune of performing a vitreoretinal fellowship at the New England Eye Center under the mentorship of Carmen Puliafito, MD, MBA; Jay Duker, MD; Elias Reichel, MD; and Caroline Baumal, MD. I recall the frustration of treating many cases of exudative AMD. We were actively enrolling patients in trials for alternative photosensitizers, as the trials of verteporfin with PDT had completed enrollment. Dr. Reichel was working on an innovative approach to treatment using transpupillary thermotherapy. Dr. Puliafito was always looking for something novel, so he welcomed an opportunity to attempt use of triamcinolone in some of his patients that had not responded to traditional treatment manifesting exudative AMD.

The results we noted in a very small case series were not particularly impressive. However, optical coherence tomography (OCT) consistently showed a reduction in macular fluid levels despite often minor effects on visual acuity or angiographic neovascular ingrowth. I studied these patients carefully and hypothesized that exudative AMD may not be the best target disease for this drug therapy. There was an obvious biologic effect on the tissue, but the disease was ultimately resistant to this strategy.

I did some research on triamcinolone, pulling articles from as early as the 1970s when Robert Machemer, MD, studied intravitreal injection of this drug to reduce proliferative vitreoretinopathy. A common theme that emerged was that corticosteroids generally stabilize the blood-retinal barrier, although the mechanism for this was unclear. Some hypothesized an anti-inflammatory effect through the blockage of cytokines such as prostaglandins and leukotrienes. Others
noted an anti-VEGF effect; in fact, most of us are aware that VEGF was formerly referred to as “antipermeability factor.”

Regardless, there was general consensus that corticosteroids positively influence the blood-retinal barrier. Furthermore, it just seemed to make sense: When your knee is swollen, you may get a cortisone injection to reduce the swelling and enhance the healing. Why, then, would this class of medication not work for an edematous retina?

Finally, our current treatment appeared inadequate. Laser treatment is generally successful at preventing moderate visual loss, but it incurs significant hurdles when used in those who manifest diffuse edema and or center-involving edema with cystoid changes. Additionally, laser rarely improves vision to a significant degree.

**Case in Point**

Clear in my memory is a long-term patient from Maine who reported to Boston with progressive visual loss from diabetic macular edema (DME). She had undergone several successful focal laser treatments by Dr. Puliafito and had maintained adequate macular function for nearly 10 years. However, this time was different; her acuity had dropped several lines to the 20/400 level. She was now legally blind and was having tremendous difficulty with her daily functioning. Angiography confirmed significant diffuse macular edema, and OCT showed increased central cystoid change with massive thickening of the fovea. Dr. Puliafito turned to me and asked, “So, what do you want to do?” I thought about it and suggested an intravitreal triamcinolone injection. It would probably not be appropriate to print his initial response, but suffice it to say that he thought it was crazy idea. However, as most of us are aware, Dr. Puliafito is an innovator at heart and appreciates novel approaches to disease. He ultimately agreed to inject this first refractory DME candidate with triamcinolone.

She returned 2 days later for follow-up. The results were nothing short of phenomenal. Her vision was already improving back to baseline, and her OCT was completely restored to a normal anatomic configuration; there was not a trace of edema present under her reestablished foveal contour. She was ecstatic, and we felt we were onto something (with the understanding that N=1 does not define clinical efficacy).

**Realization**

There was actually skepticism that the OCT was wrong despite the patient’s subjective improvement. Did the technicians mix up the scans from a different eye or a different patient? When had we ever before seen macular edema disappear in a matter of hours?

In fact, the scans were real, and we repeated the treatment on several more cases of refractory DME, culminating in a 2002 publication of the first case series in *Ophthalmology*.

Then, other etiologies were entertained, including vein occlusions, postoperative cystoid macular edema, and uveitic macular edema. The treatment seemed to have positive effects to some degree in all of these potential indications.

Subsequent collaboration with Michael Ip, MD, a former New England Eye Center fellow currently on the faculty at the University of Wisconsin, led to the current National Institute of Health (NIH) sponsored trials for macular edema due to diabetic retinopathy and retinal venous occlusive disease. Ultimately, these will be pivotal trials that determine the role, if any, of this medication in the treatment of macular edema.

In the meantime, many of us will continue to be impressed with the results and use the drug off-label. Still others will incorporate more modern pharmacotherapy, such as anti-VEGF agents, into their therapeutic regimens. In any event, intravitreal injection appears to be here to stay (at least for the near term). There are also several corticosteroid sustained-release devices being evaluated that may impact our future treatment of this condition.

**Changing Practice Patterns**

Innovation can be a strange phenomenon. It is quite interesting that a cheap drug that has been around for decades can be used against label (let alone off-label) in a completely different delivery mode for a unique disease process. It would be unfair for me to take personal credit for this innovation. As mentioned earlier in this article, Drs. Danis and Ciulla (along with several European colleagues) were injecting this medicine into the vitreous cavity for exudative AMD before I could even spell it. Without Dr. Puliafito, there would have never been an opportunity to treat the first diabetic patient; I am unaware of many individuals who would have the fortitude to attempt such a procedure for the first time. The efforts of many others resulted in the “Kenalog craze” in the early 2000s. It seemed like we had a hammer and everything looked like a nail.

Purists may take offense to this approach (and many do), as the pivotal trials are still ongoing. However, it is undeniable that this treatment started a major shift in the way we think about treating medical retinal disease, not to mention the potential surgical indications.

Adam Martidis, MD, practices at the Retina Institute of California in Pasadena. He reports no financial relationships. Dr. Martidis can be contacted at: +1 626 568 8838.

Elias Reichel, MD, is Vice Chair for Research and Education, Department of Ophthalmology, at the New England Eye Center, Tufts University School of Medicine, in Boston. He is a member of the Retina Today Editorial Board and may be reached at EReichel@tufts-nemc.org.


Jul/Aug 2008 | Retina Today | 21