

Anecortave Acetate for Steroid-Induced OHT

A good idea that did not make it in clinical trials.

BY BARBARA SMIT, MD, PhD

A steroid-induced elevation in IOP represents a special situation in glaucoma. Whereas most forms of the disease require lifelong treatment, the rise in IOP caused by steroids is generally self-limited and diminishes within weeks of the cessation of steroid treatment.¹ In a small proportion of patients, the increase in IOP may be severe and uncontrolled by topical medical therapy.^{2,3} In addition, some patients may require chronic or intermittent steroid treatment and therefore longer-term IOP control. Likewise, steroids administered via injection, both intraocular and periocular, continue to affect the IOP as long as the depot of steroid remains. For example, a single intravitreal 20-mg injection of triamcinolone acetate was reported to raise the IOP for 8 months or longer.²

Trabeculectomy surgery can successfully control high IOP, but the procedure has well-known risks, including hypotony maculopathy, bleb leaks and dysesthesias, blebitis, and endophthalmitis. For patients whose IOP requires control only until the steroid-induced increase diminishes, it is particularly desirable to avoid long-term surgical complications. The individuals who require long-term treatment with corticosteroids for chronic disease may also benefit from a nonsurgical therapy that allows them to continue using these agents despite elevated IOP.

Corticosteroid-induced ocular hypertension (OHT) is also of interest as an inducible model of glaucoma that may help reveal the mechanisms and treatment of open-angle glaucoma. Although the mechanism by which glucocorticoids induce a rise in IOP remains unknown, it has long been understood that the hypertensive response occurs due to a reduction in aqueous outflow.⁴ Several genes are known to be upregulated with glucocorticoid treatment. The most studied example is the myocilin gene, which is also involved in juvenile-onset primary open-angle glaucoma (POAG).⁵ Similarities between steroid-induced OHT and POAG suggest that treatments for the former may prove relevant to the treatment of

the far more common disease of POAG. For these reasons, anecortave acetate has been investigated as a slowly released medication for steroid-induced glaucoma, but progress in this area has stalled.

ANECORTAVE ACETATE: A NOVEL APPROACH

Anecortave acetate is a cortisene, a synthetic molecule derived from cortisol acetate but devoid of glucocorticoid activity.⁶ Due to its angiostatic properties, the agent has been studied as a therapy for neovascular age-related macular degeneration.⁷ Preclinical safety pharmacology and toxicity studies found no major clinically significant ocular or systemic side effects or toxicity.⁸

Alan L. Robin, MD, spearheaded the clinical study of anecortave acetate for the treatment of glaucoma. His case series provided the first clinical reports on its potential use in controlling IOP. In a small, prospective, uncontrolled case series, the agent lowered IOP in eyes with medically uncontrolled steroid-induced OHT.⁹ This study was undertaken after an observation that a patient with neovascularization treated with an anterior injection of anecortave acetate exhibited a reduction in his IOP. The study included patients who had previously received intravitreal or sub-Tenon's injections of triamcinolone acetonide. Eight eyes of seven patients received a 0.8-mL anterior juxtasclear depot of 3% anecortave acetate solution (24 mg). The mean IOP prior to injection was 39.9 mm Hg (range, 34-57 mm Hg) and was reduced by an average of 12.0 mm Hg (29%, $P = .005$) after 1 week. One month after treatment, seven of eight eyes had a lower IOP than baseline (mean reduction, 14.1 mm Hg; 34.5%). There were no adverse events observed.

Two other case series have reported an IOP-lowering effect of juxtasclear injections of anecortave acetate for glaucoma. The drug (24 mg) significantly lowered IOP in

six of seven eyes with POAG by 40% to 50% at 1 month and a baseline IOP ranging from 23 to 52 mm Hg.¹⁰ Prata and others treated 28 patients who had either open- or closed-angle glaucoma with anecortave acetate (30 mg) using a similar injection technique.¹¹ The mean baseline IOP of 30.7 mm Hg dropped to 21.3 mm Hg (29% reduction from baseline) at week 1 and to 21.7 mm Hg (27.2%) at month 3. Only minor adverse events were reported, including small subconjunctival hemorrhages in four cases after injection and one transient corneal dellen.

Additionally, an animal model has been used to investigate the suppression of corticosteroid-induced OHT.¹² Corriedale sheep have a robust and consistent elevation in IOP after treatment with prednisolone acetate or triamcinolone acetonide. In this study, both eyes of 16 sheep were treated with topical prednisolone. One eye of each sheep was treated with a sub-Tenon's injection of anecortave acetate or vehicle, either concurrent with the initiation of steroid therapy or 10 days after the induction of elevated IOP (eight eyes in each treatment group).

The IOP of eyes treated with prednisolone and vehicle rose approximately 2.4-fold higher than baseline. The IOP of eyes treated with anecortave acetate concurrent with the initiation of prednisolone treatment remained at baseline levels until around day 43, when the pressure began to rise. By day 66, the IOP of both sets of eyes was equivalent. Among the animals that were treated with anecortave acetate after they had developed increased IOP from prednisolone's administration, the IOP dropped back to baseline levels after treatment with anecortave acetate. Outflow facility was measured in both groups and found to be consistently higher in the animals treated with anecortave acetate and prednisolone relative to the prednisolone-only group. This research shows that anecortave acetate can both preserve and restore aqueous outflow facility in this animal model for corticosteroid-induced OHT.

CURRENT STATUS

The described reports all support the idea that anecortave acetate may be an effective moderate-term treatment for OHT related to corticosteroids or, potentially, for other forms of glaucoma. Because anecortave acetate has been used as a depot or slowly released treatment of IOP, it might eliminate the daily need for eye drops. Consequently, there has been interest in this drug as a possible means of avoiding problems related to patients' adherence to topical medical therapy. In addition, therapy with anecortave acetate may provide a treatment paradigm for the study of the cause of reduced trabecular outflow facility in eyes with elevated IOP.

Clinical trials by Alcon Laboratories, Inc. (Fort Worth, TX), had been underway to investigate the efficacy of this drug for the treatment of POAG. In July 2009, the company announced that it was discontinuing these trials after an analysis of phase 2 clinical data. The mean reduction from baseline IOP at 3 months after a single anterior juxtasceral injection of 60 mg of anecortave acetate was 3.8 mm Hg. The manufacturer, however, reported that the responder rate and the degree of IOP lowering were not sufficient to continue trials of the drug.¹³ This decrease in IOP was comparable to what one might expect from a topical carbonic anhydrase inhibitor or selective beta blocker.

Although published data were promising regarding the efficacy of this medication for steroid-induced OHT, the decision to suspend trials for the treatment of POAG means that, at least for now, this therapeutic option is no longer being widely investigated. Perhaps treatment with anecortave acetate will be revisited as researchers investigate new methods of drug delivery for glaucoma. □

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