Reduction of Intraocular Pressure With Anecortave Acetate in Eyes With Ocular Steroid Injection–Related Glaucoma

Alan L. Robin, MD; Eric P. Suan, MD; Raymond N. Sjaarda, MD; David G. Callanan, MD; Joseph DeFaller, PhD†; for the Alcon Anecortave Acetate for IOP Research Team

Objective: To evaluate the intraocular pressure (IOP)—lowering potential of anecortave acetate (AA) in eyes with steroid-related ocular hypertension inadequately controlled with the maximal tolerated or appropriate medical therapy.

Design: Uncontrolled case series.

Methods: A total of 8 eyes of 7 subjects with medically uncontrolled IOP following intravitreal or sub-Tenon injections of triamcinolone acetonide were included. All received an 0.8-mL anterior juxtascleral depot of 3% AA solution (24 mg) under topical anesthesia. The IOP was assessed weekly for the first month, then monthly for a minimum of 1 year.

Results: The mean baseline IOP was 39.9 mm Hg. After 1 week, the mean IOP decreased 12 mm Hg (29%; \( P = .005 \)) and by 1 month, the mean IOP had decreased 14.1 mm Hg (34.5%; \( P = .003 \)) from baseline. Four eyes required surgical intervention despite a decrease in IOP because of markedly elevated initial IOP and the degree of preexisting glaucomatous optic neuropathy. We observed no adverse events.

Conclusions: An anterior juxtascleral depot of AA lowers IOP substantially in some eyes with medically uncontrolled steroid-related ocular hypertension. Further study is warranted to clarify the role of AA in treating this condition as well as other forms of glaucoma.


INTRAVITREAL ADMINISTRATION of triamcinolone acetonide has become routine in the treatment of numerous vascular conditions of the posterior segment including neovascular age-related macular degeneration and macular edema from a variety of causes. Corticosteroid-related ocular hypertension is a well-recognized complication of intravitreal triamcinolone acetonide therapy. In studies of intravitreal triamcinolone for various disease states, the incidence of elevated intraocular pressure (IOP) of more than 21 mm Hg was approximately 40% within 9 to 10 months of injection. Anecortave acetate (AA) is a novel synthetic molecule derived from cortisol (Figure 1). Cortisol’s 11β-hydroxyl group is replaced with a double bond between carbons 9 and 11, and an acetate group is added at carbon 21; the resulting molecule is referred to as a cortisene. This modification renders the molecule free of all glucocorticoid and mineralocorticoid activity. Anecortave acetate possesses antiangiogenic activity via inhibition of the proteases necessary for vascular endothelial cell migration and has been evaluated as a potential therapy for neovascular age-related macular degeneration.

We have previously used an anterior juxtascleral depot (AJD) injection of AA in a diabetic patient with neovascular glaucoma in his only remaining eye, and noted both regression of anterior segment neovessels and a remarkable and enduring reduction of IOP. Subsequently, we had a similar experience in a patient with steroid-related ocular hypertension resulting from an intravitreal injection of triamcinolone acetate. Herein we report our experience treating a series of 8 eyes of 7 subjects with steroid-related ocular hypertension using AA.

METHODS

This was a prospective uncontrolled case series conducted under an Investigator’s Investigational New Drug Application (IND 60219) obtained from the Food and Drug Administration by an investigator (A.L.R.). The study was reviewed and approved by the Sterling institutional review board. All participating subjects provided written informed consent. The study adhered to the tenets of the Treaty of Helsinki and the Health Insurance Portability and Accountability Act.
The 7 subjects included in this article were recruited consecutively from one referral glaucoma practice. All had ocular steroid injections between 2 and 4 months prior to enrollment in this study. There was no apparent difficulty in patient recruitment, as all were potential surgical candidates. To be eligible for participation, subjects had to be aged 18 years or older and diagnosed with an injectable steroid-related ocular hypertension that was poorly controlled despite being given the maximal tolerated medical therapy. Women of child-bearing potential were eligible to participate if they were not pregnant, not planning to become pregnant, had a negative urine pregnancy test, were not breast-feeding, and agreed to use a highly reliable form of birth control during the study. Subjects were excluded if any of the following criteria were met: intraocular surgery within 60 days prior (excluding triamcinolone injection); myopic retinopathy or refractive error of more than −8.00 diopters; a history of scleral buckling surgery; clinical evidence of scleral thinning; use of anticoagulation therapy other than aspirin or antiplatelet therapy; any known contraindications.

**Figure 1.** Structural comparison of the endogenous glucocorticoid cortisol and the cortisene anecortave acetate. Three structural modifications were made to cortisol to generate anecortave acetate: (1) removal of the 11-β-hydroxyl, (2) addition of a double bond between C9 and C11, and (3) addition of a 21-acetate group.

**Table 1. Demographic and Ocular Features**

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<th>Characteristic</th>
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<th>4</th>
<th>5</th>
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<td>DME</td>
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<td>DME</td>
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<td>IVTA × 1; 3</td>
<td>IVTA × 7; 33, 21, 17, 12, 7, 3, 1</td>
<td>IVTA × 9; 36, 33, 22, 17, 15, 12, 8, 6, 4, 1</td>
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<td>Trabeculectomy</td>
<td>Trabeculectomy</td>
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Abbreviations: AA, anecortave acetate; CME, cystoid macular edema; CRVO, central retinal vein occlusion; DME, diabetic macula edema; dorz/tim, dorzolamide, 2%/timolol, 0.5%; IOP, intraocular pressure; IVTA, intravitreal triamcinolone acetonide; NA, not available; STTA, sub-Tenon triamcinolone acetonide.
to therapy with steroid-related compounds; or any unstable medical condition that would preclude compliance with study visits.

Following a comprehensive ophthalmological evaluation, participating subjects were given an AJD of AA. Preparation of the ocular surface consisted of 0.5% apraclonidine and 2.5% phenylephrine to vasoconstrict conjunctival vessels and 0.5% moxifloxacin and 5% povidone iodine to sterilize the ocular surface. A small region of inferior or temporal conjunctiva was anesthetized using 2% lidocaine applied by cotton-tipped applicator. Subjects were then asked to look upward; no lid speculum was placed. We carefully injected 0.8 mL of a 3% AA suspension (24 mg) through a 30-guage needle into the anterior sub-Tenon space slowly over 1 to 2 minutes. Immediately after withdrawal of the needle, tamponade of the needle track was accomplished with a cotton-tipped applicator for several minutes to prevent reflux. Subjects were evaluated 1 hour after the procedure, then weekly for 1 month, then monthly for 1 year. At each assessment, the following were assessed: interim medical and ocular history and adverse events; best-corrected Snellen visual acuity; external examination of the eye and its adnexa; extraocular motility and/or restriction of gaze; pupil responsiveness including the presence of afferent pupillary defect; IOP; and slitlamp examination of the anterior segment and lens. At each visit during the first 3 months, we took photographs of the anterior segment and questioned the subjects regarding comfort. At the initial visit and every 6 months, gonioscopy, dilated fundus examination, and standard automated perimetry, if possible, were also performed; a urine pregnancy test was performed at each 1-month follow-up visit for women of childbearing potential.

The primary statistical endpoint for this small pilot study was the mean IOP change from baseline at each follow-up visit. Given the small number of eyes and subjects, statistical analysis is limited to descriptive statistics rather than inferential statistics.

RESULTS

A total of 8 eyes of 7 subjects were included in this study. The pertinent ocular histories and baseline characteristics of the 7 patients are given in Table 1. All had elevated IOPs, measured by the referring ophthalmologists, that were similar to those obtained at baseline.

Immediately after therapy, all subjects had a large whitish elevated blister of conjunctiva and Tenon space that extended at least 180° and was full of AA (Figure 2 and Figure 3). Within an hour, lid blinking caused the AA to distribute circumferentially for at least 270° surrounding the limbus. By the second hour, the appearance of the eye was acceptable in all 3 cases (Figure 2); this was not noticed past the first day after the injection. No patient experienced pain or more than mild discomfort. The most common elicited subjective symptom was a feeling of pressure during the injection process.

The mean IOP prior to treatment was 39.9 mm Hg (range, 34-57 mm Hg). A rapid and sustained reduction of IOP was noted as soon as 1 week after treatment with AA (Table 2 and Figure 4). After 1 week, all 8 eyes had lower IOPs than at baseline by an average of 12.0 mm Hg (29%; \( P = .005 \)). By 1 month after treatment, the mean IOP was reduced by 14.1 mm Hg (34.5%; \( P = .003 \)).

The individual course of each eye is depicted in Table 2. Although the IOP reductions seen in the first month were quite significant, 4 eyes (50%) had an IOP of 30 mm Hg or more at the 4-week visit. Because of the marked initial IOP elevation and the degree of optic nerve damage from both preexisting and steroid-related glaucoma, we performed trabeculectomies to lower the IOP even further. Of the remaining 4 eyes, 2 achieved and maintained adequate IOP control with no further intervention while 3 others experienced late IOP elevation. These latter 3 required and received additional triamcinolone depot therapy after AA therapy. Reestablishing IOP control was achieved in 2 eyes with additional AA injections.

All injections were well tolerated without injection-related complications. No adverse events were noted by any patient at any visit.
The effects of corticosteroids on IOP in both normal and glaucomatous eyes were first described more than 40 years ago in association with topical dexamethasone.10,11 Steroid-related ocular hypertension has become more commonplace in the era of intravitreal triamcinolone acetonide therapy for a variety of posterior segment conditions. Up to 40% of eyes receiving intravitreal triamcinolone will require pharmacologic therapy for IOP control.2,3,12,13

Our preliminary data suggest that there may be a role for AA in the management of severe steroid-related ocular hypertension in some eyes. Several features of AA render it suited to this application, including substantial IOP-lowering efficacy in these eyes, long duration of action with infrequent retreatments, no need for intraocular injection, and relatively excellent safety and tolerability. Additionally, the AJD may be a favorable route of administration for this medication. It delivers the medication adjacent to the sclera, the medication seems to accumulate over the trabecular meshwork (Figure 5), and AA is relatively insoluble, so it can remain in this location for a prolonged period of time.

Anecortave acetate had a rapid and profound effect on IOP in our series. Seven eyes had substantial IOP reductions within 1 week after treatment, the eighth had substantial IOP reduction at week 2 (mean reduction, 12.0 mm Hg; 29%), and 7 of 8 had IOP lower than baseline at 1 month (mean reduction, 14.1 mm Hg; 34.5%). We do not believe that the IOP decrease observed in these subjects represented regression to the mean, as there were multiple IOP measurements by the referring ophthalmologists documenting IOPs similar to our baseline measurements. Intravitreal triamcinolone produces modest IOP elevation in up to half of treated eyes and marked IOP elevation in only 5% to 10% of eyes, with less than 5% of eyes requiring IOP-lowering surgery.2,3,12,13 Thus, the IOP reduction seen in our series would likely be adequate to control IOP in most eyes with steroid-related ocular hypertension.

Active triamcinolone remains in the vitreous cavity for at least 3 months,14 and normalization of IOP following a single intravitreal triamcinolone injection can take 7 to 9 months after injection.15 In eyes that are recalcitrant to medical IOP-lowering therapy, we are often forced to apply a long-term solution—IOP-lowering surgery—to a self-limited condition. This may be more complex in many eyes, as many are pseudophakic. The duration of action of AA appears to mirror the duration of IOP perturbance following intravitreal steroid therapy. Four eyes in our series achieved clinically acceptable IOP levels following AA therapy. Of these, 1 eye (patient 2) remained under control, with no further IOP interventions throughout 11 months of follow-up. The remaining 3 eyes received additional intravitreal triamcinolone injections after AA therapy, and all exhibited late IOP elevation. Patient 7 received a repeat triamcinolone injection 5 months after AA and lost IOP control 1 month later.
Patient 3’s right eye maintained adequate IOP control through 7 subsequent triamcinolone injections before losing IOP control 27 months after AA therapy; the eye was retreated with AA and IOP control was regained. Patient 3’s left eye maintained adequate IOP control through 3 additional triamcinolone injections before experiencing elevated IOP 8.5 months after AA; retreatment with AA controlled IOP through 4 more triamcinolone injections over 18 months, when another AA retreatment re-established IOP control (Figure 6). Thus, the IOP-lowering effect of AA may last up to 6 months, or up to 27 months in some eyes, despite continual reexposure to intravitreal triamcinolone. (Additionally, multiple AJDs of AA caused no untoward effects.) This interval is consistent with the 6-month retreatment schedule used in trials evaluating AA as a therapy for age-related macular degeneration.4,9

Patients in our series tolerated both the injection process and the long-term depot of AA without problems. While the possibility of globe perforation exists, no such cases occurred using the posterior juxtascleral technique required in the macular degeneration trials; it is reasonable to assume that the direct visualization afforded by anterior placement of the depot would make globe penetration unlikely. Once injected, there were no solicited or volunteered reports of adverse events associated with the drug. This is consistent with age-related macular degeneration trials in which there were no adverse events that were considered drug-related that occurred more often in eyes treated with AA than in those treated with a placebo.4,9

The mechanism by which AA lowers IOP in eyes with steroid-related ocular hypertension is unknown. When exposed to corticosteroids, numerous changes occur to...
trabecular cells at both the cellular and ultrastructural levels, including increased cell size, reduced phagocytotic activity, and increased synthesis and deposition of extracellular matrix molecules. Additionally, some cultured human trabecular meshwork cells demonstrate upregulation and increased synthesis of myocilin, a protein of unknown function. Ane cortave acetate alters trabecular meshwork cell protein and gene expression via an unidentified receptor. Glucocorticoid treatment of trabecular meshwork cells increases the expression of plasminogen activator inhibitor–1, a protein that inhibits activation of extracellular proteinases and leads to enhanced extracellular matrix deposition. Recent studies have shown that AA blocks glucocorticoid induction of plasminogen activator inhibitor–1, which may be partially responsible for AA’s IOP-lowering activity.

In summary, we have demonstrated that an AJD of AA can safely produce rapid and substantial reduction of IOP in eyes with steroid-related ocular hypertension that persists for up to 6 months or more in some subjects. The mechanism by which AA acetate lowers IOP is unknown. Further investigation is required to confirm these preliminary results, establish optimal dosing, clarify the mechanism by which the drug lowers IOP, and determine the clinical indications for the use of AA in the management of steroid-related ocular hypertension.

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Alcon Ane cortave Acetate for IOP Research Team: Abbot Clark, PhD; Gerald Cagle, PhD; Scott Krueger, PhD; Michael Bergamini, PhD; Theresa Landry, PhD; Jaime Dickerson, PhD; Sally Scheib, PhD; David Covert, MBA; Tony Realini, MD.

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REFERENCES