Anterior Juxtascleral Delivery of Anecortave Acetate in Eyes with Primary Open-Angle Glaucoma: A Pilot Investigation

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PURPOSE: To describe the intraocular pressure (IOP)-lowering effects in eyes with open-angle glaucoma (OAG) after treatment with an anterior juxtascleral depot of anecortave acetate.

DESIGN: Prospective, interventional case series.

METHODS: Seven eyes of six subjects with OAG, with uncontrolled IOP while being administered one or more topical medications, received 24 mg anecortave acetate delivered by anterior juxtascleral depot. IOP was assessed at baseline and regularly after treatment for up to 24 months.

RESULTS: Mean IOP before anecortave acetate treatment was 31.3 ± 11.3 mm Hg and dropped by 9.5 ± 4.5 mm Hg (32.7% ± 16.8%) within one week after treatment. This IOP reduction was sustained through six months (8.4 ± 5.4 mm Hg [29.6% ± 12.4%]) and 12 months (9.5 ± 5.7 mm Hg [34.9% ± 15.9%]) after a single anecortave acetate treatment. The injection process was well tolerated, and no eyes experienced any injection-related or drug-related serious adverse events.

CONCLUSIONS: Both the anterior juxtascleral depot of a drug and anecortave acetate may be promising candidates for IOP reduction in eyes with OAG. Additional studies are required to establish better their efficacy and safety, optimal dosing frequency, mechanism of action, and potential additivity to other IOP-lowering therapies.

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OPEN-ANGLE GLAUCOMA IS ASSOCIATED WITH ALMOST NO SYMPTOMS UNTIL IT REACHES THE ADVANCED STAGES. AS SUCH, THE CLINICAL MANAGEMENT OF GLAUCOMA FREQUENTLY IS COMPROMISED BY PATIENT NONADHERENCE TO THERAPY. NUMEROUS STUDIES HAVE DOCUMENTED THE PREVALENT ISSUE OF LACK OF ADHERENCE, PERSISTENCE WITH INTRAOCULAR PRESSURE (IOP)-LOWERING THERAPY, OR BOTH.1–3 ONE REASON FREQUENTLY CITED BY GLAUCOMA PATIENTS IS THE COMPLEXITY OF A MULTIDRUG REGIMEN.4 EVEN IN THE PROSTAGLANDIN ERA, 40% OF SUBJECTS WITH OCULAR HYPERTENSION STILL REQUIRE MULTIPLE MEDICATIONS TO ACHIEVE A MODEST 20% REDUCTION IN IOP.5 THE PERCENTAGE OF PATIENTS REQUIRING ADJUNCTIVE THERAPY IN ESTABLISHED GLAUCOMA IS EVEN HIGHER BECAUSE CURRENT GUIDELINES RECOMMEND A MINIMUM INITIAL IOP REDUCTION OF 25%.6

Prostaglandin analogs have become the initial therapy for ocular hypertension and glaucoma for most patients. In a sizable number, this medication alone is insufficient to control IOP adequately. Topical β-adrenergic therapy usually is considered as a first-line adjunctive therapy. Despite its advantage as being once daily with complimentary mechanisms of action, there is minimal additive effect of a β-blocker to a prostaglandin analog.7–9 Even with the addition of a topical carbonic anhydrase inhibitor or α-agonist three times daily, not much more than 2 mm Hg of IOP lowering is achieved.10 The addition of more drugs increases the costs to the patient and society and also increases the risk of side effects and preservative-related ocular surface inflammation.11 Further complicating the situation, most glaucoma patients already are using other medications for systemic diseases, adding to the overall medication burden of the patient.12 The need exists for a safe and highly effective IOP-lowering agent with an extended duration of action that reduces or eliminates patient involvement in dosing.

Anecortave acetate, an angiostatic cortisene recently evaluated as a therapy for neovascular age-related macular degeneration (AMD), may be such a candidate therapy for long-term IOP reduction. Anecortave acetate is a cortisol derivative, formed by replacing the hydroxyl group at carbon 11 with a double bond between carbons 9 and 11, and the addition of an acetate group at carbon 21.13 The resulting molecule lacks glucocorticoid activity.14,15 Anecortave acetate has been shown to possess angiostatic activity via inhibition of proteases that degrade the extracellular matrix, thus blocking migration of vascular endothelial cells,16,17 and has been studied in phase III clinical trials as a potential treatment for neovascular AMD.18,19
Unlike corticosteroids such as prednisone, dexamethasone, or triamcinolone, anecortave acetate does not reduce inflammation or cause cataracts.\textsuperscript{14} Anecortave is relatively insoluble and has been found to exert its effect near where it is delivered. To this end, a novel approach was investigated and is reported herein. This involved the use of a 30-gauge needle, under modified topical anesthesia, delivering the medication as a depot in a circumferential manner surrounding the limbus, over the trabecular meshwork (anterior juxtascleral delivery [AJD] system). This article describes a case series of seven eyes of six subjects with open-angle glaucoma (OAG), uncontrolled with at least a prostaglandin analog, who were treated with anecortave acetate using an AJD. We describe the procedure, the IOP-lowering, the duration of IOP-lowering, and adverse events.

**METHODS**

**TABLE 1. Baseline Demographics and Pertinent Ocular Histories of Participating Subjects in Anecortave-Treated Eyes with Open-Angle Glaucoma**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Eye</th>
<th>Eye color</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Race</th>
<th>Diagnosis</th>
<th>Cup-to-disc ratio</th>
<th>No. of medications</th>
<th>Baseline IOP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>Blue</td>
<td>63</td>
<td>Female</td>
<td>White</td>
<td>POAG</td>
<td>0.9</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>Blue</td>
<td>52</td>
<td>Male</td>
<td>White</td>
<td>PDS</td>
<td>0.9</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>Blue</td>
<td>65</td>
<td>Female</td>
<td>White</td>
<td>POAG</td>
<td>0.9</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>Blue</td>
<td>48</td>
<td>Female</td>
<td>White</td>
<td>POAG</td>
<td>0.9</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>Hazel</td>
<td>70</td>
<td>Male</td>
<td>White</td>
<td>PXF</td>
<td>0.6</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>Hazel</td>
<td>56</td>
<td>Male</td>
<td>White</td>
<td>POAG</td>
<td>0.5</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>Left</td>
<td>Hazel</td>
<td>56</td>
<td>Male</td>
<td>White</td>
<td>POAG</td>
<td>0.5</td>
<td>1</td>
<td>23</td>
</tr>
</tbody>
</table>

| IOP = intraocular pressure; PDS = Pigmentary Glaucoma syndrome; POAG = primary open-angle glaucoma; PXF = pseudoexfoliation glaucoma; yrs = years. |

Anecortave is relatively insoluble and has been found to exert its effect near where it is delivered. To this end, a novel approach was investigated and is reported herein. This involved the use of a 30-gauge needle, under modified topical anesthesia, delivering the medication as a depot in a circumferential manner surrounding the limbus, over the trabecular meshwork (anterior juxtascleral delivery [AJD] system). This article describes a case series of seven eyes of six subjects with open-angle glaucoma (OAG), uncontrolled with at least a prostaglandin analog, who were treated with anecortave acetate using an AJD. We describe the procedure, the IOP-lowering, the duration of IOP-lowering, and adverse events. Let therapy, any known contraindications to therapy with steroid-related compounds, or any unstable medical condition that would preclude compliance with study visits. Subjects were not washed out of prior prostaglandin analogs or other topical or systemic glaucoma medications, but were discontinued from all prior glaucoma therapy with the exception of a prostaglandin analog (which was continued during this study) at the time of treatment with anecortave acetate.

After a comprehensive ophthalmologic evaluation, consenting subjects received an AJD of anecortave acetate. Approximately 20 minutes before the AJD, the ocular surface was pretreated with both 0.5% apraclonidine and 2.5% phenylephrine to vasoconstrict conjunctival vessels. Topical proparacaine was administered, followed by topical 0.5% moxifloxacin and topical 2.5% povidone iodine to minimize the risk of infection. A cotton-tipped applicator was saturated with topical proparacaine and was applied to the inferior conjunctiva for approximately one minute. Subjects then were instructed to look upward. A 30-gauge needle was introduced into the subconjunctival space bevel down until the investigator was sure it was in the sub-Tenon space. Its position was monitored throughout the procedure. Through this 30-gauge needle, 0.8 ml 3% anecortave acetate solution (24 mg) was injected into the anterior sub-Tenon space slowly over one to two minutes. The injections were all video recorded. Subjects were questioned after the AJD regarding comfort. They were asked to return in one hour to insure that there was no IOP elevation. They then were evaluated weekly for the first month, and then monthly thereafter for up to two years. All IOP measurements were obtained at approximately the same time of day. Baseline IOP measurement was a mean of two separate IOP measurements. The investigator was not masked to either the treatment or the treated eye. Assessments included changes in medical and ocular history and solicitation of adverse events; photo-
graphs of the eye and sclera for the first three months; best-corrected Snellen visual acuity evaluation; external examination of the eye and its adnexae; extraocular motility, restriction of gaze, or both; pupil responsiveness including the presence of afferent pupillary defect; slit-lamp examination of the anterior segment and lens; gonioscopy; dilated fundus examination at six-month intervals; IOP measurement using Goldmann tonometry; and standard automated perimetry annually.

The primary statistical endpoint for this small pilot study was mean IOP change from baseline at each follow-up visit. A one-tailed $t$ test (null hypothesis, mean $\text{IOP}_{\text{treated}} \geq \text{mean IOP}_{\text{baseline}}$ vs alternative hypothesis, mean $\text{IOP}_{\text{treated}} < \text{mean IOP}_{\text{baseline}}$) was performed for each time point. A maximum of one eye from each subject was included in the analysis. Because both eyes for Subject 6 were treated, a separate $t$ test was carried out at each time point including either the right or left eye for Subject 6.

**RESULTS**

WE ENROLLED A TOTAL OF SEVEN EYES OF SIX SUBJECTS. The baseline characteristics and pertinent ocular histories of these seven eyes are given in Table 1. All summary statistics and analyses were calculated using only one eye from each patient (including only the right eye from Subject 6). These were repeated using the left eye, which yielded similar results.

The mean IOP before treatment with anecortave acetate was 31.3 ± 11.3 mm Hg. The seven treated eyes were using a mean of 1.7 ± 1.5 medications (range, one to four medications) at baseline. Anecortave acetate therapy produced a rapid and substantial reduction in IOP (Table 2; Figure 1). Within one week of treatment, mean IOP dropped by 9.5 ± 4.5 mm Hg (32.7% ± 16.8%). By four weeks after treatment, the mean IOP dropped by 12.7 ± 8.1 mm Hg (39.23% ± 17.6%). These IOP reductions were sustained through six months (8.4 ± 5.4 mm Hg [29.6% ± 12.4%]) and 12 months (9.5 ± 5.7 mm Hg [34.0% ± 15.9%]) after a single anecortave acetate treatment.

Most eyes demonstrated a substantial reduction in IOP after anecortave acetate therapy, but not all achieved adequate IOP control, despite large IOP reductions. The IOP in Subject 5’s right eye dropped from 52 to 27 mm Hg (a 25 mm Hg [48.1%] reduction) within four weeks of

![Figure 1](image-url)
the subjects were controlled by a single administration of anecortave acetate and having OAG with IOP control, with an IOP of less than 21 mm Hg, being considered successful therapy. Note that Subject 6 is considered separately for the right eye included (dashed line) and left eye included (solid line).

FIGURE 2. Kaplan-Meier survival analysis in eyes treated with anecortave acetate and having OAG with IOP control, with an IOP of less than 21 mm Hg, being considered successful therapy. Note that Subject 6 is considered separately for the right eye included (dashed line) and left eye included (solid line).

anecortave acetate treatment, but still was higher than target with three topical medications; this eye underwent trabeculectomy without any complications and with good IOP control two years after surgery. Subject 2’s right eye demonstrated no appreciable response to anecortave acetate therapy; IOP remained within 2 to 3 mm Hg of its 29 mm Hg baseline, and ultimately required two additional topical medications at month 4 to achieve adequate control.

Table 2 and Figure 1 provide data through 12 months after a single injection of anecortave acetate. Five eyes (four patients) were observed through up to 24 months of follow-up. Subject 1, who was able to discontinue her single topical medication four months after treatment, remained controlled, with IOPs of 20 mm Hg or less with no medications at all visits through 24 months. Subject 3, who began the study with an IOP of 36 mm Hg with four medications, maintained an IOP of 20 mm Hg or less with no further IOP-lowering interventions through 19 months of follow-up after anecortave acetate therapy. Subject 4 was able to discontinue prostaglandin monotherapy three months after anecortave acetate therapy, required that it be restarted 11 months after therapy, and remained controlled with IOP of 15 mm Hg or less for a total of 19 months after anecortave acetate treatment. Subject 6 received anecortave acetate therapy to both eyes, with adequate IOP control until 13 months after treatment, when IOP in each eye rose to 28 mm Hg. Both eyes were retreated with anecortave acetate 24 mg, after which IOP in both eyes remained at 20 mm Hg or below through 11 more months of follow-up (24 months total).

Using 21 mm Hg and a 20% reduction from baseline as an arbitrary threshold for adequate IOP control, two-thirds of the subjects were controlled by a single administration of 24 mg anecortave acetate for 12 months (Subject 6’s right eye included), or 50% of subjects if Subject 6’s left eye was used. This difference is because the right eye for Subject 6 had an IOP of 20 mm Hg at month 3 (13% reduction from baseline), returning to 16 mm Hg at month 5. In contrast, the left eye had IOPs in the teens until the 12-month visit. These results are depicted in a Kaplan-Meier plot in Figure 2. All injections were well tolerated without injection-related complications. One subject had a vasovagal episode, but later reported having similar events when having blood drawn. All reported a pressure sensation associated with the injection that lasted at most for a few hours. No serious adverse events were noted by any subject at any visit.

DISCUSSION

FOR THOSE PATIENTS WHO REACH GLAUCOMA END-STAGE disease and eventually blindness, it is estimated that the costs for benefits, healthcare, and reduced tax revenues total $1.5 billion per year. Many other costs can be associated with increasing visual impairment. These include the costs associated with decreased ability to complete daily activities, increased falls, increased risk of car accidents and increased mortality. Therefore, the use of an anterior juxtascleral administration of anecortave acetate may have the potential to preclude or delay the progression of this chronic disease process and may have a significant positive impact on the economic and psychological burden of glaucoma.

Intraocular pressure reduction is the only treatment that has been established to lower the risk of glaucomatous progression. Numerous highly effective methods of IOP reduction are available, including medications, laser therapy, and surgical interventions. Medications typically are used as first-line therapy, with a wide variety of medications and combinations from which to choose. Successful medical therapy, however, is dependent on patient adherence to prescribed treatment regimens, and there exist many important barriers limiting such adherence. The consequence of inadequate treatment arising from patient nonadherence is disease progression, characterized by permanent and irreversible loss of visual function. Although there is no direct consistent evidence linking nonadherence with progression of disease, there are suggestions that nonadherence can affect outcomes in subjects with glaucoma. There is also evidence in other medical fields that adherence to therapy can affect outcomes.

Glucoma drug discovery and development peaked in the mid 1990s with the introduction of three new classes of topical IOP-lowering medications: the topical carbonic anhydrase inhibitors, adrenergic agonists, and prostaglandins, all within two years. Since then, several same-class drugs and one combination of existing drugs have been introduced, but no new innovation in drug class for IOP-lowering has emerged in more than a decade. IOP-lowering drug delivery, still limited to daily topical instil-
Anecortave acetate represents a potential innovation in both drug class and drug delivery for glaucoma management. In this small pilot case series, anecortave acetate demonstrated substantial IOP-lowering ability. Its pericellular safety when injected as a posterior juxtascleral depot already has been established in United States FDA phase III trials for AMD, and it was well tolerated when injected as an anterior juxtascleral depot by all eyes in this and our steroid-related ocular hypertension series. The mechanism by which anecortave acetate lowers IOP is unknown, but the magnitude, rapidity, and duration of IOP reduction after a single anterior juxtascleral depot injection are remarkable.

In this series, we demonstrated that anecortave acetate significantly lowered IOP in six of seven eyes with OAG and that its effect lasted for at least three months and up to 19 months. Notably, the percent IOP reduction was comparable throughout the IOP spectrum, lowering IOP by a consistent 40% to 50% at four weeks in eyes with baseline IOP ranging from 23 to 52 mm Hg. Retreatment was successful in both eyes of Subject 6, dropping IOP by 8 to 9 mm Hg within two weeks and maintaining this reduction at seven months after retreatment. All injections were well tolerated and cosmetically acceptable by one hour after injection. These favorable observations support a potential role for anecortave acetate in the management of chronic glaucoma.

The mechanism of anecortave acetate’s IOP-lowering ability currently is not fully understood. Glucocorticoids and the growth factor transforming growth factor (TGF)-β2 have been implicated in glaucoma pathogenesis. Glucocorticoid treatment can cause elevated IOP in humans, animals, and in an ex vivo perfusion-cultured anterior segment model. Likewise, elevated TGF-β2 also can elevate IOP in perfusion-cultured anterior segments as well as in mice transduced with a TGF-β2 expression vector (Shepard AR, et al, unpublished data, 2008). We have been examining the effects of treating cultured human trabecular meshwork (TM) cells with the glucocorticoid dexamethasone as well as TGF-β2 to understand better how these insults alter TM cell gene expression. Both of these agents increase the messenger ribonucleic acid (mRNA) and protein expression of plasminogen activator inhibitor-1 (PAI-1) in TM cells. PAI-1 plays a major role in extracellular matrix metabolism because it directly inhibits the activation of pro–matrix metalloproteinases. Inhibition of these extracellular proteinases increases deposition of extracellular matrix in the TM, which are features of both glucocorticoid-induced and TGF-β2-induced ocular hypertension as well as primary open-angle glaucoma (POAG).

Transduction of mouse eyes with an adenovirus PAI-1 expression vector elevates IOP (Pang I-H, unpublished observation, 2007), demonstrating that increased expression of PAI-1 in the anterior segment can be pathogenic. The elevated PAI-1 expression induced by either dexamethasone or TGF-β2 in cultured TM cells can be inhibited in a dose-dependent manner by concomitant addition of anecortave desacetate in the culture medium, which at least in part may be responsible for this agent’s ability to lower IOP in glaucoma- and steroid-induced ocular hypertensive patients. The EC50 for this inhibition of PAI-1 expression is approximately 100 to 500 μm (Clark AF, unpublished observation, 2007).

Limitations of this series include its very small number of eyes and the lack of any control data. As such, general statements regarding the efficacy and safety of this novel treatment for IOP reduction are not possible. It may be that the IOP reduction in part was the result of regression to the mean, observer bias, or increased adherence to IOP-lowering medications after the AJD. It also may be that the actual act of the injection caused the IOP to be diminished.

The possible safety of this method also can not be appreciated fully by this limited number of subjects. Complications such as scleral perforation with secondary hemorrhage, cataract formation, or endophthalmitis certainly are not likely, but are possible.

In summary, anecortave acetate may be a promising candidate for IOP reduction in eyes with POAG. The drug offers the potential for substantial IOP reductions, and its mode of delivery—via an anterior juxtascleral depot—offers the potential for longer-term IOP control without the requirement of daily therapeutic adherence by patients. Future studies are required to establish better the efficacy and safety of anecortave acetate administered as an anterior juxtascleral depot injection for the reduction of IOP. The focus is on eyes with OAG to determine the optimal dosing and duration of action and to establish its mechanism of action and potential additivity to other available IOP-lowering treatments.
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Biosketch

Alan L. Robin earned his bachelor’s degree at Yale University, New Haven, Connecticut, and his MD at Tufts University, School of Medicine, Boston, Massachusetts. He trained in ophthalmology at the Greater Baltimore Medical Center, and in glaucoma with both Harry A. Quigley, MD, and Irvin Pollack, MD at the Wilmer Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland. Dr Robin was awarded the 2005 American Academy of Ophthalmology Outstanding Humanitarian Service Award. His current interests are clinical glaucoma, adherence and execution of glaucoma therapies, novel treatments for glaucoma, and international ophthalmology.
Abbot F. Clark received his PhD in cellular and molecular biology at Case Western Reserve University in Cleveland, Ohio and did his post-doctoral training in immunology and physiology at the University of Texas Southwestern Medical Center in Dallas, Texas. He worked for more than 20 years in Ophthalmic Discovery Research at Alcon Laboratories in Fort Worth, Texas and just recently joined the University of North Texas Health Science Center in Fort Worth, where he is Professor of Cell Biology & Genetics and Director of the Visual Sciences Program. Dr Clark continues to explore the cellular and molecular pathogenic mechanisms for glaucoma and other ocular diseases.