Anecortave Acetate (15 Milligrams) versus Photodynamic Therapy for Treatment of Subfoveal Neovascularization in Age-Related Macular Degeneration

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Purpose: To compare 1-year safety and efficacy of anecortave acetate 15 mg with photodynamic therapy (PDT) with verteporfin in patients eligible for initial PDT treatment.

Design: Prospective, masked, randomized, multicenter, parallel group, active control, noninferiority clinical trial.

Participants: Five hundred thirty patients with predominantly classic subfoveal choroidal neovascularization secondary to age-related macular degeneration were randomized to treatment with either anecortave acetate 15 mg or PDT.

Methods: In the anecortave acetate group, the drug was administered under the Tenon's capsule as a periocular posterior juxtascleral depot (PJD) at the beginning of the study and at month 6. Before the first administration of anecortave acetate, patients in this treatment group received a sham PDT treatment, and sham PDT treatments were repeated every 3 months if there was evidence of leakage on fluorescein angiography (FA). Patients assigned to PDT received up to 4 PDT treatments at 3-month intervals, as needed based upon FA, and a sham PJD procedure at the beginning of the study and at month 6. Best-corrected visual acuity was determined at baseline and all follow-up visits. Safety data were regularly reviewed by an independent safety committee.

Main Outcome Measure: Percent responders (patients losing <3 lines of vision) at month 12.

Results: Percent responders in the anecortave acetate and PDT groups were 45% and 49%, respectively (not statistically different, $P = 0.43$). The confidence interval (CI) for the difference ranged from −13.2% favoring PDT to +5.6% favoring anecortave acetate. The month 12 clinical outcome for anecortave acetate was improved in patients for whom reflux was controlled and who were treated within the 6-month treatment window (57% vs. 49%; 95% CI, −4.3% favoring PDT to +21.7% favoring anecortave acetate). No serious adverse events related to the study drug were reported in either treatment group.

Conclusions: The safety and efficacy outcomes in this study demonstrate that the benefits of anecortave acetate for the treatment of choroidal neovascularization outweigh the risks associated with either the drug or the PJD administration procedure. *Ophthalmology 2006;113:3–13 © 2006 by the American Academy of Ophthalmology.*

Although neovascularization is a normal physiologic process and is essential for wound healing, aberrant choroidal vascular growth beneath the retina and/or the retinal pigment epithelium causes irreversible retinal damage in age-related macular degeneration (AMD).

Anecortave acetate is an angiostatic agent administered as a periocular posterior juxtascleral depot (PJD) for treatment of choroidal neovascularization. During the synthesis of anecortave acetate (Alcon Research, Ltd., Fort Worth, TX), there were specific and permanent changes made to the original cortisol structure resulting in the creation of an angiostatic cortisene that inhibits blood vessel growth and does not exhibit glucocorticoid receptor–mediated activity in vivo either preclinically or clinically.[1]

Anecortave acetate has demonstrated efficacy in 14 in vitro and in vivo models of neovascularization[2–5] (Murray et al. Subconjunctival anecortave acetate, an angiostatic steroid, in the treatment of a murine model of retinoblastoma. Abstract presented at: Association for Research in Vision and Ophthalmology meeting, April, 2003; Ft. Lauderdale, Florida) (Murray et al. Combined anti-angiogenic

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and peri-ocular chemotherapy using anecortave acetate and carboplatin in the treatment of retinal tumors in the LHbetaTag murine transgenic model of retinoblastoma. Abstract presented at: Association for Research in Vision and Ophthalmology meeting, April, 2004; Ft. Lauderdale, Florida).

In contrast to other antiangiogenic agents like vascular endothelial growth factor inhibitors and protein kinase C inhibitors, anecortave acetate inhibits angiogenesis irrespective of the initiating angiogenic signal, a mechanism that likely explains the broad-spectrum angiostatic nature of this compound in numerous tissues and species[2–5] [Bingaman et al. Local delivery of anecortave acetate inhibits laser-induced choroidal neovascularization (CNV) in the mouse. Abstract presented at: Association for Research in Vision and Ophthalmology meeting, April, 2004; Ft. Lauderdale, Florida].

The 24-month clinical data (Kaiser et al. Trans-scleral administration of anecortave acetate administered in patients with subfoveal AMD—24 month clinical outcomes. Presented at: American Academy of Ophthalmology Meeting, November, 2003; Anaheim, California) from the dose response study (C-98-03) confirmed the efficacy and safety of anecortave acetate seen at month 12.[6] Patients treated with anecortave acetate 15 mg maintained significantly better vision than patients treated with a placebo after 12 months (79% vs. 53%, responders, $P = 0.03$) and 24 months (73% and 47%, $P = 0.03$), in predominantly classic and minimally classic choroidal neovascularization lesions. In view of these positive long-term safety and efficacy outcomes, this phase III comparison of anecortave acetate 15 mg (Retaane 15 mg [anecortave acetate suspension], Alcon Research Ltd.) with photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis AG, Bülach, Switzerland) for treatment of subfoveal choroidal neovascularization (C-01-99) was undertaken, and the 12-month results are reported.

Materials and Methods

This was a prospective, randomized, double masked, multicenter, parallel group, active control, noninferiority clinical trial at 52 sites in the United States, Canada, Europe, Israel, and Australia. The study was designed to evaluate the efficacy and safety of anecortave acetate 15 mg versus PDT in patients eligible for PDT treatment who had not previously been treated with PDT. It is a 12-month study with an additional 12-month follow-up with continued masked treatment as per the original randomization assignment. The study was reviewed and approved by an institutional review board or independent ethics committee for each site, and all patients read and signed an informed consent document before participating in the study (and, in the U.S., signed an addendum for the Health Insurance Portability and Accountability Act after it was enacted). Key inclusion and exclusion criteria defining patient eligibility are shown in Table 1, and a list of study personnel is in the "Appendix."

Randomization

Five hundred thirty patients were randomized in a 1:1 ratio to receive either anecortave acetate 15 mg (n = 263) or PDT with verteporfin (n = 267) within 7 days after completing all screening procedures. Patients randomized into the study had a diagnosis of exudative AMD in their study eye, subfoveal choroidal neovascularization eligible for treatment with PDT, and no prior treatment with PDT. Patients were classified by the Digital Angiography Reading Center (New York, New York)[6] before randomization as having predominantly classic choroidal neovascularization (≥50% of the total lesion was classic choroidal neovascularization) and a total lesion size of ≤5400 μm in its greatest linear dimension.

Table 1. Inclusion and/or Exclusion Criteria for the Study

- Inclusion criteria
  - Patients were at least 50 yrs old.
  - Patients could be of any race or gender.
  - A clinical diagnosis of exudative age-related macular degeneration (AMD) and a primary or recurrent (after laser photocoagulation) subfoveal choroidal neovascularization lesion in the study eye. The lesion must have had the characteristics defined below:
    - A lesion area of ≤5400 μm in its greatest linear dimension.
    - ≥50% of the total lesion (defined as angiographic evidence of neovascularization, associated contiguous areas of serous elevation of retinal pigment epithelium, elevated blocked fluorescence, and/or late staining) was choroidal neovascularization.
    - The classic component of the total choroidal neovascularization must have been at least 50% of the total lesion.
  - A best-corrected Early Treatment Diabetic Retinopathy Study visual acuity (VA) of 0.30 (20/40 Snellen) to 1.30 (20/400 Snellen) in the study eye at the screening visit.
- Exclusion criteria
  - History of any medical condition that would preclude scheduled study visits or completion of the study.
  - History of ophthalmic disease in the study eye that would likely compromise, or during follow-up would likely compromise, the VA of the study eye.
  - Clinical signs of myopic retinopathy or a refraction of >−8-diopter power in their current prescription.
  - Photodynamic therapy treatments of any kind in the study eye. Previous thermal laser photocoagulation in the study eye was allowed, if performed at least 30 days before enrollment in the study.
  - Intraocular surgery in the study eye within 60 days before enrolling in the study.
  - A scleral buckle in the study eye.
  - Previous experimental procedure (or treatment) or systemically administered antiangiogenic therapy for exudative AMD in either eye, including anecortave acetate treatment of the fellow eye. Radiation treatment in the study eye (previous proton beam radiation in the fellow eye was allowed). Previous experimental photodynamic therapy treatment in the patient's fellow eye, before enrollment in the study, was allowed.
  - Use of any investigational drug or treatment related or unrelated to AMD within 30 days before receipt of study medication excluding daily vitamin and/or mineral therapy.
  - A known medical history of allergy or sensitivity to the steroid family of drugs, to verteporfin, and/or to fluorescein dye that was clinically relevant in the investigator's opinion.
  - Patients whose screening fluorescein angiographic images could not be adequately visualized by the investigator and the Digital Angiography Reading Center.
  - IV or subcutaneous anticoagulant therapy, or patient was on oral anticoagulant therapy (with the exception of aspirin and antiplatelet therapy) and could not take a 5-day interruption in therapy before *each* administration procedure.
  - A medical history of porphyria.
  - Clinical evidence of scleral thinning.

Study Treatments

Patients randomized to the anecortave acetate 15 mg group received a sham PDT treatment at the baseline visit before the