European Journal of Ophthalmology / Vol. 15 no. 4, 2005 / pp. 482-485

Anecortave acetate for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration

U. SCHMIDT-ERFURTH, S. MICHELS, R. MICHELS, A. AUE

Department of Ophthalmology, University of Vienna, Vienna - Austria

PURPOSE. Anecortave acetate is a novel angiostatic cortisene being evaluated clinically for treatment of exudative age-related macular degeneration (ARMD). A randomized, placebo-controlled, efficacy and safety dose duration study of anecortave acetate for depot suspension (3 mg, 15 mg, 30 mg) in this patient population was completed in June 2003. As part of this trial, 128 patients with subfoveal choroidal neovascularization (CNV) secondary to ARMD were enrolled and treated for up to 2 years by 18 clinical sites in the United States and European Union.

METHODS. Study patients were evaluated clinically with detailed ophthalmic examinations, general physical examinations, assessments of best-corrected logMAR visual acuity, and angiographic evaluations. The Digital Angiography Reading Center (New York City, NY) assessed lesion eligibility while the clinical investigators assessed overall patient eligibility prior to treatment. As part of this study, study medication was delivered as a posterior juxtascleral depot using a specially designed curved cannula at 6-month intervals if in the masked investigator's opinion the patient's lesion could benefit from additional treatment.

RESULTS. The 2-year efficacy results of this placebo-controlled study demonstrated that RETAANE 15 mg (anecortave acetate for depot suspension) was statistically superior to placebo for stabilization of vision (<3 logMAR line change from baseline) and for inhibition of neovascular lesion growth. There were no serious treatment-related safety issues associated with either the study medication or the procedure for administration.

CONCLUSIONS. Anecortave acetate 15 mg for depot suspension is clinically efficacious compared to placebo for treatment of subfoveal exudative ARMD lesions when administered at 6-month intervals as a posterior juxtascleral depot. (Eur J Ophthalmol 2005; 15 : 482-5)

KEY WORDS. Anecortave acetate, Age-related macular degeneration, Choroidal neovascularization

Accepted: June 6, 2005

INTRODUCTION

Anecortave acetate is an angiostatic agent that acts to inhibit blood vessel growth by inhibiting the synthesis and activation of proteolytic enzymes necessary for endothelial cell migration in response to angiogenic stimulation (1, 2). It is a derivative of cortisol, but the specific and permanent chemical modifications to cortisol made during the synthesis of anecortave acetate have resulted in the creation of a unique angiostatic cortisene with no evidence of glucocorticoid receptor-mediated biological activities (3). There has been no nonclinical or clinical evidence of steroidal side effects such as elevated intraocular pressure or cataractous progression.

In June 2003 a masked, randomized, placebo-con-

1120-6721/482-04$15.00/0

trolled safety and efficacy dose-duration study of anecortave acetate for depot suspension (3 mg, 15 mg, or 30 mg) in patients with subfoveal exudative ARMD was completed. A total of 128 patients were enrolled and treated by 18 clinical sites in the United States and European Union with optional retreatment every 6 months if the masked investigator determined that the patient's CNV lesion could benefit. The month 6 and month 12 results from this safety and efficacy dose-duration study demonstrate the superiority of anecortave acetate 15 mg for depot suspension over placebo when administered as a posterior juxtascleral depot directly onto the outer surface of the sclera with a specially designed curved cannula (4, 5). These data have recently been confirmed by the month 24 analyses. Based on these supportive data, a trial is now underway with enrollment complete to evaluate RETAANE 15 mg versus photodynamic therapy with Visudyne, and two international trials comparing RETAANE 15 mg to placebo treatment are now enrolling patients.

MATERIALS AND METHODS

This dose-duration safety and efficacy study enrolled 128 patients at 18 United States/European Union sites and randomized them in masked fashion to either placebo or to one of three doses of anecortave acetate (30 mg, 15 mg, or 3 mg). IEC/IRB approval of the study was obtained prior to patient screening at each of the clinical sites, and patients signed an IEC/IRB-approved informed consent prior to treatment. The study medication (anecortave acetate for depot suspension or placebo) was administered as a posterior juxtascleral depot onto the scleral surface by a masked investigator with specially designed curved cannula. Key eligibility inclusion and exclusion criteria are detailed in Appendix 1, and principal investigators for the study are listed in Appendix 2. Screening assessments for eligibility included a general physical examination, a detailed ophthalmic examination, and an assessment of best-corrected logMAR visual acuity as described previously (4, 5).

The Digital Angiography Reading Center (DARC, New York City, NY) assessed CNV lesion eligibility prior to treatment. All lesion evaluations in this study were made in masked fashion by two trained retina expert readers at the DARC. All other assessments of patient eligibility were made by the participating clinical investigators. The decision as to need for additional administrations of masked study medication was made by the masked investigator at months 6, 12, and 18. Patients were exited from the study if additional administrations were not needed in the masked investigator's opinion. The last data collected for patients exiting prior to the month 24 visit were carried forward into the analysis of subsequent visits using the last observation carried forward procedure as described previously (4, 5).

Clinical safety was assessed during this study with periodic physical and detailed ophthalmic examinations, and the safety data were periodically reviewed by an Independent Safety Committee overseeing the study. Clinical efficacy was evaluated using logMAR visual acuity testing and evaluations by the Digital Angiography Reading Center of fluorescein angiographic CNV lesion changes over time.

RESULTS

Analysis of the clinical outcomes at month 24 demonstrate that treatment with RETAANE 15 mg is statistically superior ($p<0.05$) to placebo at month 24 for stabilization of vision. Stabilization of vision is defined for this study as a change from baseline vision of less than 3 logMAR lines. Whereas patients in the placebo group showed a mean decrease from baseline logMAR vision of more than 3 lines at month 24, patients in the RETAANE 15 mg group showed a mean decrease of about 1.5 logMAR lines, a difference which is also statistically significant ($p<0.05$). This analysis also revealed the statistical superiority of RETAANE 15 mg compared to placebo for inhibition of lesion growth ($p<0.05$). Patients treated with RETAANE 15 mg exhibited an increase at month 24 of about 100% in the measurable area of the CNV lesion component in digital fluorescein angiograms. In contrast there was an increase of about 350% in the area of this lesion component over the same period following placebo treatment. The parameters used in this study were central visual acuity and angiographic lesion growth. Both features were influenced by the treatment and responded positively. The correlation of functional and anatomic findings supports the defined mechanism of action of the drug, i.e., an antiangiogenic property. Clearly, additional diagnostic modalities such as indo-

cyanine green angiography (ICGA) and particularly optical coherence tomography (OCT) are of great value in such studies, but were not part of the protocol at that early stage.

No clinically relevant drug-related or administration-related adverse events have been identified to date by the Independent Safety Committee, nor has this Committee identified any clinical evidence of glucocorticoid activity following anecortave acetate administration. More than 300 posterior juxtascleral administration procedures were performed during this study, using the same superotemporal quadrant of the orbit. As part of this study, 81 patients received at least two administrations of anecortave acetate for depot suspension (all doses), and 48 patients received four. The procedure of a juxtascleral depot compares extremely favorably with more invasive techniques such as intravitreal injections. Endophthalmitis, traumatic cataract, as well as retinal detachment were seen in a substantial number in studies using an intravitreal drug application. The critical issue, however, is the control of an exact deposition of the compound at the posterior pole of the eye. Any reflux through the entrance site as well as a malposition anteriorly or laterally should clearly be avoided. The recommended interval of retreatment of 6 months provides an excellent base for a treatment strategy in a chronic disease process where reinjections in short intervals represent a substantial burden for the patient, the treating ophthalmologists, and reimbursement issues. However, the correct drug application and maintenance of a standardized retreatment schedule will represent crucial issues for this technique.

DISCUSSION

Formal evaluations of both the month 6 and month 12 clinical outcomes from this ongoing study were completed in 2002, and the results of these evaluations have been published (4, 5). The data presented here confirm these earlier analyses. When compared to posterior juxtascleral depot administrations of placebo, administration of RETAANE 15 mg using the same procedure demonstrated clinical efficacy for stabilization of visual acuity and inhibition of growth of the pre-existing subfoveal neovascular lesion. RETAANE 15 mg administered as a posterior juxtascleral depot every 6 months in this completed study was well tolerated, with no clinically relevant drug-related or administration-related side effects identified by the investigator, an Independent Safety Committee, or Alcon Product Safety.

In view of the positive clinical safety profile and the demonstrated clinical efficacy of RETAANE 15 mg for treatment of subfoveal exudative ARMD, a trial is now being initiated to evaluate the efficacy of anecortave acetate 15 mg and 30 mg for depot suspension for reducing the risk of progression to exudative ARMD in patients with nonexudative ARMD at risk for progression to this blinding disorder.

ACKNOWLEDGEMENTS

Clinical trial activities funded by Alcon Research, Ltd., Fort Worth, TX, as part of a Phase III clinical trial.

APPENDIX 1

Key inclusion criteria:

- Age ≥ 50 years.
- Exudative ARMD and primary/recurrent subfoveal CNV ≤ 30.48 mm^2 (arithmetic equivalent of 12 MPS disc areas) in size. Angiographic evidence that CNV occupies at least 50% of the total lesion area. The area of CNV must be composed of at least 50% classic CNV, or the area of the classic CNV must be at least 1.6 mm^2 (arithmetic equivalent of 0.75 MPS disc areas).
- Best-corrected ETDRS visual acuity of 0.3 (20/40 Snellen equivalent) to 1.2 (20/320 Snellen equivalent) in the study eye at the eligibility visit. The fellow eye must have clinical evidence of macular degeneration, with a visual acuity of 1.6 (20/800 Snellen equivalent) or better.
- Willing to give and sign informed consent; able to make the required study visits.

Key exclusion criteria:

- Medical history or clinical evidence of pre-existing ophthalmic disease in the study eye (other than ARMD) that during follow-up would likely compromise the visual acuity of the study eye.
- Clinical evidence of myopic retinopathy, or a refraction of >-8 diopter power.
- Intraocular surgery in study eye less than 2 months prior to enrolling.
- History of previous experimental treatment for ARMD in the study eye other than laser photocoagulation.
- Presence of a scleral buckle in the study eye.
- Use of any investigational drug or treatment related or unrelated to ARMD within 30 days prior to enrollment.
- Medical history of a bleeding disorder or need for anticoagulant therapy other than antiplatelet therapy.
- Clinical evidence of scleral thinning.

APPENDIX 2

Participating principal investigators:

Stephen Russell, MD – University of Iowa Medical School, Iowa City, IA, USA.

Lawrence J. Singerman, MD – Retina Associates of Cleveland, Cleveland, OH, USA

Lawrence A. Yannuzzi, MD – Vitreous-Retina-Macula Consultants of New York, New York, NY, USA

Allen C. Ho, MD – Wills Eye Hospital, Philadelphia, PA

Bernard Godley, MD, PhD, Erik Van Kuijk, PhD, MD – Univ. Texas Medical Branch, Galveston, TX, USA

Martin Friedlander, MD, PhD – Scripps Institute, La Jolla, CA, USA

Mary Lou Lewis, MD, Philip Rosenfeld, MD, PhD – Bascom Palmer Eye Institute, Miami, FL, USA

Kurt Gitter, MD – Retina Associates, New Orleans, LA, USA

Gisele Soubrane, MD – Universitaire de Creteil, Creteil, France

Gary Edd Fish, MD – Texas Retina Associates, Dallas, TX, USA

Steven Schwartz, MD – Jules Stein Eye Institute, Los Angeles, CA, USA

Kevin Blinder, MD – Barnes Retina Institute, St. Louis, MO, USA

Henry Hudson, MD – Retina Centers, Tucson, AZ, USA

Andrew P. Schachat, MD – Wilmer Ophthalmological Institute, Baltimore, MD, USA

Marc D. de Smet, MD – Academic Center University of Amsterdam, Amsterdam, The Netherlands

Ursula Schmidt-Erfurth, MD, PhD – University Eye Hospital Luebeck, Luebeck, Germany

Felix Sabates, MD – Truman Medical Center, Kansas City, MO, USA

Mark Blumenkranz, MD – California Vitreoretinal Research Center, Menlo Park, CA, USA

Reprint requests to:
Ursula Schmidt-Erfurth, MD
Professor and Chair
Department of Ophthalmology
University of Vienna
Waehringer Guertel 18-20
A-1090 Wien, Austria
ursula.schmidt-erfurth@meduniwien.ac.at

REFERENCES

1. Clark AF. AL-3789: a novel ophthalmic angiostatic steroid. Exp Opin Invest Drugs 1997; 6: 1867-77.
2. Penn JS, Rajaratnam VS, Collier RJ, Clark AF. The effect of an angiostatic steroid on neovascularization in a rat model of retinopathy of prematurity. Invest Ophthalmol Vis Sci 2001; 42: 283-90.
3. McNatt LG, Weimer L, Yanni J, Clark AF. Angiostatic activity of steroids in the chick embryo CAM and rabbit corneal pocket models of neovascularization. J Ocul Pharmacol 1999; 15: 413-23.
4. Anecortave Acetate Clinical Study Group. Anecortave acetate as monotherapy for the treatment of subfoveal lesions in patients with exudative age-related macular degeneration (ARMD): interim (month 6) analysis of clinical safety and efficacy. Retina 2003; 23: 14-23.
5. Anecortave Acetate Clinical Study Group. Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: the twelve-month clinical outcomes. Ophthalmology 2003; 110: 2372-83.