Potential Beneficial Effect of Low Dose Danazol In Combination With Renin Angiotensin Inhibitors in Diabetic Macular Edema: a 12-week Double Blind Randomized Controlled Trial

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INTRODUCTION:

In 2012, 29 million Americans had diabetes, and 1.1 and 2.1 million had DME. If left untreated, DME can result in irreversible loss of vision, and result in a lowered quality of life.

The standard treatment modality for DME is intravitreal injections of anti-VEGF agents (VEGF). One of the principal reasons for the use of anti-VEGF therapy is DME, stems from its ability to address one of the main outputs of vision loss, vascular permeability.

Danazol, a currently approved synthetic androstane ring of 17 alpha-atlastosterone, also has potential to be an effective treatment modifier for DME due to its strengthening effects on vascular permeability at arbitrarily low doses.

In 2007, we published the results of a study examining a sublingual potentiator, showing danazol decreasing endothelial cell proliferation and preventing capillary-like structures from forming. We recently discovered a biphasic effect of danazol on the retinal endothelial barrier in vitro. Danazol was discovered to amplify barrier function at nanomolar concentrations, and was associated with the reorganization of PECAM-1 cytoplasmation to form cortical actin rings, and increased intracellular interendothelial adhesion, these elements ultimately lowered vascular permeability.

Subsequent clinical trials supported the hypothesized beneficial effect of low-dose danazol, and highlighted a specific relationship with body mass index (BMI).

The objectives of the current study were to examine the data on the primary Phase 2 clinical trial, and evaluate the efficacy and safety of low-dose danazol for the treatment of DME, and to identify a potential target population for treatment with low-dose danazol for future confirmatory trials.

METHODS:

Study Design:

• Double-blind, randomized controlled trial.
• 21 study sites across the USA.
• Enrollment began February 26, 2013, and ended June 30, 2014.
• 12-week double-blind phase.
• The conduct of this trial was in accordance with the Declaration of Helsinki. The trial was prospectively approved by Liberty IRB and was retrospectively registered at ClinicalTrials.gov (NCT01618677).

All enrolled subjects provided written informed consent.

Major Inclusion Criteria:

• Patient provided written informed consent.
• ≥18 years of age with DME.
• BCVA letter score 24–78; definite central retinal thickness ≥250 μm on spectral-domain OCT due to DME.
• Focal photocoagulation can be deferred safely for 12 weeks.

Major Exclusion Criteria:

• Blood pressure >180/110 mmHg.
• HbA1c greater than 11%.
• History of treatment for DME at any time in the 8 weeks before randomization (such as focal/grid/pan retinal photocoagulation, intravitreal or peribulbar corticosteroids, anti-VEGF drugs, or any other treatment).
• Substantial cataract.
• Aphakia.

Treatment groups:

• 0.5mg danazol/BMI per day
• 1mg danazol/BMI per day
• Placebo

Outcome Measures:

• The primary outcome of the trial was change in best corrected visual acuity (BCVA) from baseline to the end of the double-blind phase.
• The secondary outcome was change in central retinal thickness (CRT), measured with optical coherence tomography (OCT), μm from baseline to the end of the double-blind phase.

Statistical Analyses:

• We assessed efficacy with a repeated measures, mixed model analysis of covariance (ANCOVA), adjusting for baseline values of BCVA and CRT and utilizing a compound symmetry covariance structure. Adjustments for multiplicity were done using the Dunnett method.
• An analysis of the interaction between treatment groups and mean double-blind BMI was done using a repeated measures analysis of covariance, adjusting for baseline CRT and BCVA, and including an interaction term for mean BMI quartile and treatment group.

RESULTS:

A total of 354 subjects (242 eyes) were randomized to one of the treatment arms. 35 (10%) subjects did not complete the trial (Figure 1).

Furthermore, we explored the effect of concomitant use of RAS inhibitors (angiotensin receptor blockers [ARB] or angiotensin converting enzyme [ACE] inhibitors) at baseline.

A fast observation carried forward approach was used for missing data. Outlining changes from baseline in BCVA values were truncated to 3 standard deviations from the mean for each treatment group. Unlike the primary and secondary outcomes, there were no adjustments for multiple comparisons in subgroup analyses as these were exploratory, aimed at identifying subgroups of patients who benefited from treatment, and for planning future confirmatory studies.

• An alpha level of 0.05 was used for all tests.

Effect of Body Mass Index

Over 88% of subjects enrolled in this study were considered overweight or obese according to the World Health Organization classification [BMI >24.9 kg/m2] (Table 1).

The effect of BMI on change in BCVA and CRT is shown in Figure 3. The 0.5mg of a on a concomitant RAS inhibitor, significantly increased from baseline in BCVA were observed at each level in the 0.5mg/danazol group (Figure 3). Furthermore, this group showed a significant 0.6 letter increase in BCVA in 12 weeks from baseline (p=0.001) than the 1.1 letter, non-significant increase from baseline to week 12, observed in the placebo group (Figure 3).

In subjects on a concomitant RAS inhibitor, both the 0.5mg and 1mg danazol/BMI treatment groups showed significant differences from baseline in CRT (p<0.05) (Table 2). The decrease in the 0.6mg danazol/BMI group was significantly greater than the 1.0信 ultrasound increase seen in the placebo group (p=0.05).

CONCLUSIONS:

The combination of oral RAS inhibitors and low dose danazol might be a painless, safe, and efficacious therapy for a subset of patients suffering from DME. Confirmatory studies of these observations are needed to test the effectiveness of low-dose oral therapy and to construct a dosing algorithm that makes treatment with low dose danazol effective for all BMI groups, not just a narrow range.

DISCUSSION:

Michael Singer has the following relationships to disclose: Ampio Pharmaceuticals, Inc.; and own stock options in Ampio Pharmaceuticals, Inc. David Bar-Or holds numerous patents on danazol and vascular permeability control; Alejandro Orlando is an independent contractor for, and holds stock options in Ampio Pharmaceuticals, Inc.

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