A Randomized Controlled Trial Comparing the Effect of Topical Dorzolamide-Timolol versus Placebo Combined with Intravitreal Anti-Vascular Endothelial Growth Factor (VEGF) Injections in Patients with Neovascular Age-Related Macular Degeneration Who Are Incomplete Anti-VEGF Responders

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INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (VEGF) agents, including bevacizumab, ranibizumab, and aflibercept, remain the standard of care treatment for neovascular age-related macular degeneration (AMD).[1–4] Various treatment modalities using these agents have been proposed, including monthly, pro re nata, and treat-and-extend regimens.[5,6] Despite frequent and consistent treatment with anti-VEGF therapy, there is a subset of patients who are incomplete responders and have persistent exudation, including intraretinal edema, subretinal fluid (SRF), and/or retinal pigment epithelial detachment (PED) on spectral-domain optical coherence tomography (SD-OCT).[7,8]

Clinical Data

While clearance of intravitreal anti-VEGF drugs is not completely understood, some studies have suggested that outflow through the anterior chamber may play a role.[9-12] We hypothesized that by decreasing aqueous production, outflow may also be reduced which could subsequently slow the clearance of intravitreal drugs. In a prior pilot study with 10 eyes of 10 patients who were incomplete responders with neovascular AMD, the effect of topical dorzolamide-timolol in combination with continued intravitreal anti-VEGF injections was explored.[13] Patients were kept on the same anti-VEGF drug as well as the same interval between injections for the 2 visits before enrollment and through the course of the pilot study in order to minimize the chances that any changes noted might be the result of altering one of these variables. The mean central subfield thickness (CST) decreased from 419.7 μm at enrollment to 334.1 μm at the final visit (p=0.012). Mean maximum subretinal fluid (SRF) height decreased from 126.6 μm at enrollment to 56.5 μm at the final visit (p=0.020). This decrease in mean CST and SRF was significant beginning at the first visit after initiation of the drops.

Trial Rationale

Based on this initial pilot data, dorzolamide-timolol appears to be a promising adjuvant treatment in combination with anti-VEGF injections for incomplete anti-VEGF responders with neovascular AMD. However, since there was no control group in the pilot study, it is possible that the decreased exudation seen was a result of the continued anti-VEGF therapy alone rather than an effect of the topical therapy. As a result, a randomized, placebo-controlled clinical trial will be better able to assess the efficacy of dorzolamide-timolol in this setting.

TRIAL OBJECTIVES

Objective

The objective of this study is to compare the efficacy of adding topical dorzolamide-timolol versus a topical placebo in combination with intravitreal anti-VEGF injections in patients with neovascular AMD who are anti-VEGF incomplete responders.

Endpoints

Primary Efficacy Endpoint:
The primary efficacy endpoint is change in mean central subfield thickness (CST) on spectral domain optical coherence tomography (SD-OCT) from baseline to the final visit.

Secondary Endpoints:
The secondary endpoints are change in mean maximum subretinal fluid height (SRF), mean maximum pigment epithelial detachment (PED) height, mean intraocular pressure (IOP) and mean pinhole Snellen visual acuity from baseline to final visit.

TRIAL DESIGN

Subjects will be randomized in a 1:1 ratio to the following groups:

- Topical dorzolamide-timolol 1 drop in study eye twice daily
- Topical artificial tears (placebo group) 1 drop in study eye twice daily

Subjects in both groups will continue to receive the same anti-VEGF drug at the same interval (± 1 week) as the 2 visits prior to study enrollment. Once enrolled, subjects will continue on the same drop as initially assigned (dorzolamide-timolol or artificial tears) for the entire study duration starting at baseline and continuing through 3 follow-up visits.

PROCEDURES

Vision Testing

Pinhole Snellen visual acuity will be obtained at each visit.

Tonometry

Tonometry will be performed using either a Tonopen or Goldmann applanation at each visit. If the IOP is ≥ 25 mm Hg, Goldmann applanation tonometry must be used to verify the reading.

Ophthalmologic Examination

The following examination will be performed at the baseline visit.

- Inspection of the eyelids
- Examination of the extra-ocular muscle movement
- Inspection of the cornea
- Examination of the anterior chamber for inflammation
- Examination of the pupils
- Examination of the iris
- Inspection of the lens
- Inspection of the vitreous body
- Inspection of the retina and optic disc

Optical Coherence Tomography

Spectral domain optical coherence tomography will be performed at all timepoints. Tracking features should be enabled to allow direct comparison of a given B-scan from one visit to another. In addition, the scan algorithm must allow for automated generation of the central subfield (1 mm circle) thickness.

SUBJECT POPULATION

Sample Size

Approximately 50 subjects will be enrolled in the study.

Inclusion Criteria

1. Active choroidal neovascularization (CNV) due to AMD.
2. Prior treatment with at least 4 injections of anti-VEGF agents in the past 6 months and persistent intraretinal and/or subretinal fluid on SD-OCT at each visit during this period.
3. Baseline CST ≥ 270 μm on SD-OCT automated retinal thickness map.
4. Injection of the same anti-VEGF agent (ranibizumab or aflibercept) at each of the two visits immediately preceding study enrollment.
5. Time interval of 5 weeks (± 1 week) between visits for at least two visits immediately preceding study enrollment.
6. Subjects of either gender aged ≥ 45 years.
7. Provide written informed consent
8. Ability to comply with study and follow-up procedures and return for study visits.

Exclusion Criteria

1. Anticipated use of intravitreal bevacizumab during the study period
2. History of uveitis.
3. Presence of intraocular inflammation, significant epiretinal membrane (causing distortion of macular anatomy per investigator discretion), significant vitreomacular traction (per investigator discretion), macular hole, or vitreous hemorrhage.
4. Any ophthalmic surgery within previous 6 months, including cataract extraction.
5. Any history of vitrectomy or glaucoma surgery (e.g., trabeculectomy, tube shunt).

6. Current prescription eye drop usage (e.g., glaucoma drops, corticosteroid drops, etc.).
7. Any contraindication for topical use of a beta-blocker (e.g., bradycardia, decompensated heart failure, chronic obstructive pulmonary disease, reactive airway disease, asthma, etc.).
8. Any history of sulfonamide allergy.

TRIAL CONDUCT

Subjects should adhere to the scheduled study visits which will take place at the same interval (± 1 week) that they were being injected between the visit prior to enrollment and the enrollment visit (i.e., every 4, 5, or 6 weeks).

Overview of Study Assessments

Assessment	Baseline	Study Visit 1*	Study Visit 2*	Study Visit 3*
Informed Consent	**X**			
Medical & Ophthalmic History	**X**			
Vision Testing	**X**	**X**	**X**	**X**
Tonometry	**X**	**X**	**X**	**X**
Ophthalmologic Examination	**X**			
Optical Coherence Tomography	**X**	**X**	**X**	**X**
Randomization	**X**			
Subjects Randomized to Dorzolamide-Timolol Reminded to Use Drops and Given Bottle	**X**	**X**	**X**	
Subjects Randomized to Artificial Tears Reminded to Use Drops and Given Bottle	**X**	**X**	**X**	

*Interval between each visit will be based upon the interval between the visit prior to enrollment and the enrollment visit. Subjects should be encouraged to follow-up at this same interval (± 1 week) for the duration of the study.

Study Assessments

The following evaluations will be performed at the visits specified below.

Baseline (Day of Enrollment in Study)

Pre-injection

- Vision testing
- Ophthalmologic examination and tonometry
- Optical coherence tomography

Injection

- *Optional if patient consents separately*: Aqueous humor sample prior to anti-VEGF injection

- Intravitreal injection of same anti-VEGF drug used at the two visits prior to enrollment (i.e., ranibizumab or aflibercept).

Post-injection

- Instruct patient on use of topical drop (dorzolamide-timolol vs. artificial tears as assigned at randomization, 1 drop twice daily for study duration) to begin same day.

Study Visit 1

Pre-injection

- Vision testing and tonometry
- Optical coherence tomography

Injection

- *Optional if patient consents separately*: Aqueous humor sample prior to anti-VEGF injection
- Intravitreal injection of same anti-VEGF drug used previously (i.e., ranibizumab or aflibercept).

Post-injection

- Instruct patient on continuing use of topical drop (dorzolamide-timolol vs. artificial tears as previously assigned, 1 drop twice daily for study duration) to begin same day.

Study Visit 2

Pre-injection

- Vision testing and tonometry
- Optical coherence tomography

Injection

- Intravitreal injection of same anti-VEGF drug used previously (i.e., ranibizumab or aflibercept).

Post-injection

- Instruct patient on continuing use of topical drop (dorzolamide-timolol vs. artificial tears as previously assigned, 1 drop twice daily for study duration) to begin same day.

Study Visit 3

Pre-injection

- Vision testing
- Ophthalmologic examination and tonometry
- Optical coherence tomography

Aqueous Humor Samples (optional)
Anterior chamber (aqueous humor) samples will be collected from all patients who provide additional consent to participate. Where patient consents to aqueous humor sampling, all efforts should be made to collect a baseline aqueous humor sample on the Baseline visit and Study Visit 1.

Withdrawal from Trial
Subjects have the right to withdraw from the trial at any time for any reason. The investigator also has the right to withdraw subjects from the trial in the event of concurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violations, cure, administrative or other reasons.

STATISTICAL METHODS

Experimental Design
This is a randomized clinical trial in which 50 subjects will be randomly assigned to receive topical dorzolamide-timolol or artificial tears (1 drop twice daily for the study duration) in combination with continuing intravitreal anti-VEGF injections for neovascular AMD.

Sample Size
Assuming a power of 0.9 and an alpha of 0.05, approximately 44 patients will be required to demonstrate a CST improvement of 400 to 350 microns with a standard deviation of 50 microns. Estimating a 10% drop out rate, approximately 50 patients will be targeted for enrollment.

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