Combination Therapy with Dietary Zeaxanthin for Neovascular Age-Related Macular Degeneration. A Randomized Clinical Trial

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Abstract

Purpose: A previous comparative interventional study suggested oral zeaxanthin added to triple therapy of intravitreal bevacizumab, intravitreal corticosteroids and photodynamic therapy with verteporfin for the treatment of neovascular age-related macular degeneration (NVAMD) was comparatively effective and cost-effective. A randomized clinical trial was undertaken to confirm these effects.

Methodology: A two-year, triple-blinded, randomized clinical trial enrolled 144 participants (168 eyes) with NVAMD to triple therapy (TT) (intravitreal bevacizumab, reduced-fluence photodynamic therapy and intravitreal dexamethasone) or the same triple therapy with oral zeaxanthin (TTZ) supplementation, 20 mg daily. Data were modeled out to the 11-year life expectancy of the average participant.

Results: At 24-months, twenty-seven percent (17/62) of TTZ eyes gained ≥ 15 letters, versus 9% (7/81) of TT eyes (p=0.003). Among unilateral, NVAMD participants, NVAMD developed in 23% (12/53) of TT and 6% (3/47) of TTZ fellow eyes with atrophic age-related macular degeneration (AMD) (p=0.02) by 24 months after baseline. The incremental cost-utility ratio of oral zeaxanthin supplementation was a remarkably low $30/QALY (quality-adjusted life-year). Zeaxanthin supplementation to TT is cost-effective in every country since the 11-year cost of TTZ ($14,486) exceeds the cost of TT ($14,480) by only $6, yet provides a 0.200 QALY gain.

Conclusion: Oral zeaxanthin supplementation of triple therapy for the treatment of neovascular age-related macular degeneration is comparatively effective because it yields improved vision and reduces the incidence of subsequent neovascular age-related macular degeneration in fellow eyes with atrophic age-related macular degeneration by 74%. Oral zeaxanthin supplementation is very cost-effective in the U.S. and worldwide referent to most ophthalmic interventions.

Keywords: Triple therapy; Neovascular age-related macular degeneration; Zeaxanthin

Introduction

Age-related macular degeneration (AMD), primarily neovascular AMD (NVAMD), is the leading cause of legal blindness in the United States [1]. Vascular endothelial growth factor A (VEGF-A) is a contributory factor to the development of NVAMD [2,3]. Other factors, such as platelet-derived growth factor (PDGF-B) may also be involved in the angiogenic process [4].

Multiple NVAMD treatment modalities exist, though each has drawbacks. Photodynamic therapy with verteporfin (PDT) targets choroidal neovascularization, but incites an injured cell response [5,6]. Intravitreal corticosteroids have an anti-inflammatory rationale [7,8], but can cause glaucoma and cataract [9]. The mainstay of NVAMD therapy is the current time is monotherapy with intravitreal VEGF-inhibitor injections, though cost and/or frequent intravitreal injection are burdens. Numerous clinical trials have demonstrated that intravitreal VEGF-inhibitor injections benefit NVAMD [10-15]. Change to "The primary major trials include the MARINA. (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab in the treatment of Neovascular AMD) Trial [10], the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) Trial [11] and the CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) Study. [12] MARINA and ANCHOR evaluated ranibizumab [10,11], CATT [12] assessed bevacizumab and ranibizumab, and a Cochrane Database Review [13] defined the benefit of aflibercept clinical trials for NVAMD. The NVAMD one-year treatment results were essentially the same with ranibizumab, bevacizumab and aflibercept, with a 6-10 letter improvement in vision [10-13]. Nonetheless, the improvement likely decreases over time [14].

Studies have also evaluated NVAMD triple therapy, specifically PDT, and intravitreal VEGF-inhibitor and corticosteroid therapy [7,8]. Our recent comparative interventional study assessing triple therapy (TT) and triple therapy with oral zeaxanthin supplementation (TTZ) demonstrated TT comparative effectiveness and cost-effectiveness [15]. Adding oral zeaxanthin reduced NVAMD incidence in fellow eyes and was more comparatively effective and cost-effective yet. Studies have found higher dietary and serum levels of lutein and xanthophyll carotenoid zeaxanthin (Zx) are associated with lower odds ratios of AMD [16-21]. The AREDS (Age-Related Eye Disease Study) Research

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Group [21] observed that higher Zx and lutein dietary intake reduced progression of both atrophic AMD and NVAMD.

To further assess the benefit of triple therapy versus triple therapy with oral zeaxanthin supplementation, [15] we undertook a randomized clinical trial to evaluate the preference-based comparative effectiveness and incremental cost-effectiveness of zeaxanthin supplementation for NVAMD triple therapy.

Methods

Primary outcomes

The primary trial outcomes were the 3-line ETDRS (Early Treatment Diabetic Retinopathy Study) gain and the cost-utility ratio (CUR) associated with two cohorts with subfoveal NVAMD that received TT or TTZ. Diagnostic modalities for NVAMD included optical coherence tomography (OCT) at each visit, as well as intravenous fluorescein angiography (IVFA) and/or intravenous indocyanine green (ICG) angiography as needed.

Design and setting

The triple-blind, randomized clinical trial was performed at the authors' offices, with enrollment from February 2012 through April, 2014. Data completion occurred in April, 2016. Participants were randomized per their social security numbers (odd=TT, even=TTZ). The treating physician was blinded to therapy, as were acuity technicians. Participants were unaware whether they received zeaxanthin, 20 mg PO daily [22] or placebo. Readers of the diagnostic modalities were also blinded to therapy.

Inclusion criteria

Included were consecutive participants ≥ 50 years of age with subfoveal NVAMD who could choose conventional VEGF-inhibitor monotherapy or VEGF-inhibitor therapy as part of triple therapy to hopefully reduce treatment frequency. The latter were enrolled in the trial described herein. Baseline visions ranged from 20/25 to 20/20,000 (hands motions at 3 feet). Macular blood, subretinal fluid, sub-RPE (retinal pigment epithelial) fluid, and/or hard exudate were typically present. OCT confirmed subretinal fluid, sub-RPE fluid and retinal edema. Intravenous fluorescein angiography and/or ICG angiography were obtained, as needed, to confirm the presence of NVAMD.

Exclusion criteria

Eyes with predominantly fibrotic NVAMD were excluded, as were eyes with choroidal neovascularization >12 disc areas. Blood was not an exclusion factor unless >12 disc areas. The absence of posterior segment drusen in either eye and/or RPE changes consistent with atrophic AMD were exclusion criteria, as was NVAMD treatment within three months, the presence of diabetic retinopathy or a non-AMD disease thought to prevent a three-line vision gain.

Protocol

All eyes were given a baseline TT cycle consisting of: 1.25 mg intravitreal bevacizumab, 1.0 mg intravitreal dexamethasone, 40 mg subtenon's methylprednisolone acetate within one week, and reduced-fluence PDT within two weeks. PDT utilized a 15 mg intravenous verteporfin injection followed by a 689 nm wavelength light dose of 25 J/cm² for 83 s [23,24]. Identical triple therapy was given to TT and TTZ Cohort participants, though the latter also received oral zeaxanthin, 20 mg. (Eye Promise Zeaxanthin, ZeaVision, Chesterfield, MO) for two years versus placebo. After 2 years, 20 mg of zeaxanthin was given to participants in both the TT and TTZ Cohorts.

Participants were re-examined at 4-6 weeks. If stable, follow-up was undertaken every 6-8 weeks in year 1 and 8-12 weeks in year 2. Retreatment was based on residual/recurrent subretinal blood, sub-RPE/subretinal/intraretinal fluid, decreased vision, IVFA leakage, or an ICG angiographic occult plaque. Triple therapy was repeated when retreatment was given.

Statistics

The chi-square test compared the categorical variable of fellow eye progression to NVAMD. When cell frequency was ≤ 5 for a contingency table category, Fisher's Exact Probability Test was utilized (Vassar Stats@ http://vassarstats.net/tab2x2.html). Linear variables, such as vision, were compared using the Student's t-test. (Microsoft Excel, Bellevue, Washington). Significance was presumed to occur at p<0.05. For bilateral NVAMD-treated participants, the two eye results per patient were not averaged, but analyzed independently.

Power calculation

A power calculation (Schoenfeld D. http://hedwig.mgh.harvard.edu/sample_size/fisher/js/fisher.html) utilizing previous data [21] determined that 70 eyes per cohort were needed, using a two-tailed, 0.05 α, to have an 80% chance of demonstrating a 20% absolute risk reduction in three-line ETDRS vision gain between the two cohorts. The study was halted when at least 70 eyes were reached in each cohort.

The Economic Model

A Value-Based Medicine (standardized) cost-utility analysis model quantified incremental and average cost-utility ratios (CURs) [25,26]. Time tradeoff patient utilities, QALYs (quality-adjusted lifetime-years), a third-party insurer cost perspective, and average, national, 2016 Medicare Fee Schedule real costs (Table 1) were utilized. The base case was an incremental cost-utility analysis comparing TTZ Cohort therapy to TT Cohort therapy. Average cost-utility analyses compared both TTZ Cohort and TT Cohort therapies to observation.

Model time frame

The 11-year, model was based upon the average life expectancy for the mean 79-year-old participant [27]. A LOCF (last observation carried forward) methodology accounted for years 3-11. The base case assumed 11-year oral zeaxanthin usage, though sensitivity analysis examined 2-year usage.

A historical, untreated, Control Cohort was created using Shah and DelPriore data [28]. Using a Lineeweaver-Burke model of control data from six randomized, Macular Photocoagulation Study Group trials, they showed that vision deterioration in untreated NVAMD eyes correlates with time since NVAMD onset. By year 11 after onset, mean vision in untreated eyes deteriorates to 20/640 (Table 2).

First-eye, second-eye models

These models utilize the patient data-proven concept that vision-related quality-of-life most closely correlates with visual acuity in the better-seeing eye [25,26,29-34]. With the first-eye model, one eye undergoes NVAMD therapy, while the fellow eye is not yet unaffected. Patient value gain, the equivalent of patient QALY gain, occurs primarily when the second eye converts to NVAMD. With the second-eye model, the first eye already has vision loss from NVAMD and second eye treatment thus accrues immediate QALY gain. Value gain, or QALY gain, can be readily converted to percent quality-of-life gain [30,31].

The combined-eye model utilized herein integrated the weighted...
average of first-eye and second-eye models. Markov modeling (Treeage, Williamstown, MA) quantified the cumulative conversion of fellow eyes to NVAMD and subsequent QALY gain associated with the first-eye model.

**Patient preference-based comparative effectiveness**

Time tradeoff utilities acquired from >1,100 ophthalmic patient interviews were utilized to quantify utility gain [34-36]. With excellent validity [35] and reliability [36] these utilities have been employed in peer-reviewed papers by the authors [21,29,31,37] and multiple other researchers [38]. They are typically unaffected by age, gender, level of education or systemic comorbidities [32-34].

Using the 11-year life expectancy, [27] we calculated the QALYs accrued by the mean TTZ Cohort and TT Cohort participant. Adverse events included the disutility associated with intravitreal injection [21]. No cases of endophthalmitis occurred. PDT adverse events accrued a 0.002 QALY loss [39].

**Cost-utility analysis**

The outcome was $/QALY (dollars expended per QALY gained), the cost-utility ratio. QALY accruals and costs were discounted at 3% per year [40].

The study was registered with ClinicalTrials.gov (Identifier: NCT 01527435) on January 27, 2012.

**Results**

Among the 139 baseline enrollees, 60% (84/139) were women and 40% (55/139) were men. Age ranged from 52-94 years, with a 79-year mean. All took AREDS I supplements throughout the trial [3].

<table>
<thead>
<tr>
<th>Beginning of Year</th>
<th>Triple Therapy with Zeaxanthin (TTZ cohort)</th>
<th>Triple Therapy (TT Cohort)</th>
<th>Control cohort (Shah &amp; DelPriore [28])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/125+1</td>
<td>20/100+1</td>
<td>20/100-2</td>
</tr>
<tr>
<td>2</td>
<td>20/100+1</td>
<td>20/100</td>
<td>20/200</td>
</tr>
<tr>
<td>3</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/250-2</td>
</tr>
<tr>
<td>4</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/320-2</td>
</tr>
<tr>
<td>5</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/400-1</td>
</tr>
<tr>
<td>6</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/500+1</td>
</tr>
<tr>
<td>7</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/500-1</td>
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<td>8</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/500-2</td>
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<tr>
<td>9</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/500-2</td>
</tr>
<tr>
<td>10</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/640+1</td>
</tr>
<tr>
<td>11</td>
<td>20/63-2</td>
<td>20/80</td>
<td>20/640</td>
</tr>
</tbody>
</table>

Table 2: Mean Visual Acuity in the Triple Therapy with Zeaxanthin, Triple Therapy without Zeaxanthin and Control Cohorts.
Therapy with Zeaxanthin; TT=Triple Therapy; ETDRS=Early Treatment Diabetic Retinopathy Study.

**Table 3:**

<table>
<thead>
<tr>
<th>Vision Parameter</th>
<th>TTZ cohort</th>
<th>TT cohort</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain of ≥ 3 ETDRS lines</td>
<td>27° (17/62)</td>
<td>9° (7/81)</td>
<td>0.006</td>
</tr>
<tr>
<td>Loss of ≥ 3 ETDRS lines</td>
<td>10% (6/62)</td>
<td>10% (8/81)</td>
<td>0.97</td>
</tr>
<tr>
<td>Vision gain from therapy</td>
<td>76% (47/62)</td>
<td>77% (62/81)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

**Table 4:**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Baseline contrast sensitivity</th>
<th>24-month contrast sensitivity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTZ</td>
<td>0.89</td>
<td>0.84</td>
<td>0.60</td>
</tr>
<tr>
<td>TT</td>
<td>0.93</td>
<td>0.88</td>
<td>0.66</td>
</tr>
<tr>
<td>p-value</td>
<td>0.63</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5:**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Central thickness at baseline (µm)</th>
<th>Central thickness at 24 months (µm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTZ</td>
<td>305</td>
<td>295</td>
<td>0.57</td>
</tr>
<tr>
<td>TT</td>
<td>314</td>
<td>269</td>
<td>0.0003</td>
</tr>
<tr>
<td>p-value</td>
<td>0.58</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6:**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Conversions in fellow eyes to NVAMD during the current study</th>
<th>Conversions in fellow eyes to NVAMD- Barbazetto et al. [40]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTZ cohort</td>
<td>12/53 (23%)</td>
<td>151/445 (34%)</td>
<td>0.10</td>
</tr>
<tr>
<td>TTZ cohort</td>
<td>3/47 (6%)</td>
<td>151/445 (34%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>p-value</td>
<td>0.02*</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

**Conversion of fellow eyes to NVAMD**

Twenty percent (16/80) of TT Cohort participants had bilateral NVAMD at baseline, versus 13% (8/64) of TTZ Cohort participants (p=0.33). The 24-month conversion rate from unilateral atrophic AMD to NVAMD in TTZ Cohort fellow eyes was 23% (12/53) versus 6% (3/47) in the TT Cohort (p=0.02) (Table 6). The 24-month, 23% fellow-eye conversion rate to NVAMD in our TT Cohort did not differ significantly (p=0.10) from the 34% rate of Barbazetto and colleagues [41], who studied the conversion rate to NVAMD in the ANCHOR and MARINA ranibizumab-treated cohorts. There was a fellow eye, conversion rate difference between Barbazetto data [41] and our 6% TTZ Cohort rate (p=0.001) (Table 6).
Economic Analysis

Incremental value gain

Two-year, TTZ and TT Cohort, QALY accruals disclose an incremental patient value gain of 0.200 QALY, a 2.8% quality-of-life improvement associated with Zx supplementation (Table 7). This comparison integrated: vision, first-eye model (80%) and second-eye model (20%) weighted contributions for Cohorts TTZ and TT, and the QALY gain accrued to Cohort TTZ from the decreased incidence of fellow eye NVAMD conversions referent to Cohort TT.

Average value gain

Comparing TTZ Cohort and TT Cohort outcomes to Control Cohort data demonstrated that TTZ therapy conferred a 14.7% QOL gain versus no therapy, while TT therapy conferred an 11.6% QOL gain (Table 7).

Costs

Costs included unilateral and bilateral therapy. The discounted, 11-year Zx, per-patient cost was $3,431. The costs for the therapeutic regimens are listed in Table 8. The 11-year, Cohort TTZ per-patient cost was $14,486, decreasing to $12,882 with two-year Zx administration. The 24-month, Cohort TTZ, cost distribution was: physician: 24.1%, diagnostic testing: 9.4%, non-zeaxanthin drugs: 42.1%, and zeaxanthin: 24.4%.

The 11-year, per-patient cost for Cohort TT, including incremental treatments in years 3-11 in the first-eye model due to the 11.30%, fellow eye, NVAMD annual conversion rate (vs. the Cohort TTZ 2.95% rate) was $14,480 (Table 8). The cost without extra fellow eye conversions in years 3-11 was $11,092. Thus, the cost of the extra fellow eye conversions after 24 months was $3,388. The overall 11-year, per-patient cost of Cohort TTZ therapy was $6 greater than Cohort TT therapy.

Cost-utility (cost-effectiveness)

The primary cost-utility outcome, the combined-eye, incremental cost-utility ratio for TTZ Cohort therapy referent to TT Cohort therapy was ($6/0.200=) $30/QALY (Table 9). The average cost-utility ratio (CUR) for TTZ was $15,296/QALY, while the average CUR for TT was $19,382/QALY.

Sensitivity analysis

Doubling Zx cost increased the incremental CUR for TTZ over TT to $12,225/QALY, while quadrupling the cost raised the incremental CUR to $51,497/QALY. The World Health Organization upper limit of 3x Gross Domestic Product (GDP) per capita (2015 US $167,400) for cost-effective interventions and 1 x GDP per capita (2015 US $55,800) for very cost-effective interventions are addressed (Table 10) [42,43]. The zeaxanthin daily cost could rise from ~1.00/day to $40/day and remain very cost-effective.

Discussion

Our trial showed that TTZ yielded significantly more benefit in the form of visual angle doubling than TT alone (p=0.006). The addition of Zx was also associated with 74% decreased NVAMD incidence in fellow eyes (p=0.02). Nonetheless, both triple therapy with and without Zx were very cost-effective referent to no therapy.

Anti-VEGF treatment is the current mainstay NVAMD treatment. The MARINA, [14] ANCHOR [15] and CATT [16] trials all showed ranibizumab visual benefit, with CATT noting similar bevacizumab benefit as well. A comparison of our outcomes with these others is...
difficult since these other trials treated NVAMD earlier, evidenced by 20/80 baseline vision in the MARINA [14] and ANCHOR [15] trials and 20/63 vision in the CATT trial [16] comparing bevacizumab and ranibizumab, versus 20/100-20/125 herein. Earlier monotherapy, as characterized by baseline NVAMD treatment when the vision is 20/80 or better, was noted to yield mean long-term vision of 20/40, better than later treatment when the baseline vision was ≤ 20/160 [44,45]. The latter visual outcome was a mean 20/160. Our 2-year, 4-letter TT Cohort gains was similar to the 5-6 letter bevacizumab and ranibizumab gains in the treatment as needed arm of the CATT Study [46]. Nonetheless, the mean 12-letter gain in our TTZ Cohort suggests possible greater benefit than in the CATT Trial for bevacizumab and ranibizumab. We didn't evaluate VEGF-inhibitor monotherapy for NVAMD, but suspect Zx adds benefit in that context as well.

We calculated CATT Study 11-year costs utilizing ranibizumab and bevacizumab of $55,629 and $11,797, respectively [16,46]. Integrating
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the combined-eye, $3,388 extra cost of fellow eye treatment obviated from years 3-11 by utilizing Zx in the the TTZ cohort, the combined-eye, TTZ participant, 11-year cost was $11,098, 7.4% less than the $11,797 bevacizumab treatment prn arm cost in the 2-year CATT Study [46].

Population-based data support our beneficial zeaxanthin results. The POLA study [47] noted high plasma lutein and Zx reduced advanced AMD risk by 79% and NVAMD risk by 93% (p=0.005). Others have noted comparable results [5,48]. The AREDS2 Research Group, [7] studied 4,203 participants with high late AMD risk and found a lutein/zeaxanthin combination more effective than zinc [49].

Macular zeaxanthin accumulates at a 2:1 ratio over lutein [50]. Its blue-light filtering effect protects the outer retina against metabolic insult. Zeaxanthin consumes singlet oxygen, possibly neutralizing free radicals from retinal metabolism [50]. Increased levels also inhibit VEGF levels [51,52]. Humans do not synthesize Zx, but consume it in fruits, vegetables and egg yolks. The American diet provides ~1mg/day, versus the 20 mg dose in our trial [53].

Economic Analysis

Cost-effectiveness

Zx supplementation has an extraordinarily cost-effective, incremental CUR of $30/QALY. The average CUR of TTZ and TT for NVAMD are also both very cost-effective. TT with an average CUR of $19,382/QALY is cost-effective by WHO criteria in 160 of the 230 world countries [41,42]. Zeaxanthin supplementation to TT is cost-effective in every country since the 11-year cost of TTZ ($14,486) exceeds the cost of TT ($14,486) by only $6, yet provides a 0.200 QALY gain.

Limitations

The lack of 11-year primary data is a drawback, though assuming Zx confers no benefit after 24-months still results in a favorable CUR (Table 10). Participants received free Zx and placebo, but there was no guarantee of 100% compliance [54]. Some trials have counted pills, though we question its efficacy. Wireless pill containers might ensure greater compliance, but were unavailable to us.

Conclusions

In summary, our clinical trial confirms the results of an earlier non-randomized study that showed NVAMD triple therapy is comparatively effective and cost-effective. Triple therapy supplementation with oral Zx is very cost-effective, further improving vision and reducing NVAMD incidence.

Acknowledgement

The study was supported in part by unrestricted grants from ZeaVision, Inc. to The Retina Center of St. Louis County and the Center for Value-Based Medicine. DL Gierhart has intellectual property rights around zeaxanthin. RJ Olk has phantom shares in ZeaVision. G. Brown and M. Brown are shareholders in the Center for Value-Based Medicine. The sponsor played no role in performing the trial, analyzing the results or altering the manuscript.

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