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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 at 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/cm^2 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 life-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 Lineweaver-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

Intervention	CPT code	Cost per treatment
Verteporfin dye for PDT	J3396	$1,634
Intravitreal bevacizumab, 1.25 mg	J9035	$72
Intravitreal dexamethasone, 1 mg	J1100	$0.12
Photodynamic therapy physician fee	67221	$290
Intravitreal injection of medication	67028	$103
Fundus photography	92250	$79
Intravenous fluorescein angiography	92235	$111
Indocyanine green angiography	92240	$257
Optical coherence tomography	92134	$45
Ophthalmological services, medical examination and evaluation	92004	$151
Ophthalmological services, medical examination and evaluation	92012	$86
Ophthalmological services, medical examination and treatment	92014	$126
*Eye Promise Zeaxanthin, Zea Vision, 20 mg per day, one-year cost	NA	$360

Table 1: National Average Medicare Fee Schedule (2016 U.S. Nominal Dollars). (PDT=Phto Dynamic Therapy with Verteporfin, CPT=Current Procedural Terminology, the interventional classification utilized by Medicare; NA=Not Applicable, *=not included within the Medicare CPT codes).

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

Table 2: Mean Visual Acuity in the Triple Therapy with Zeaxanthin, Triple Therapy without Zeaxanthin and Control Cohorts.

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 SSM Health Care Institutional Review Board approved the trial (approval number 14-07-0540). It adhered to the Helsinki Declaration and it revisions and HIPAA (Health Insurance Portability and Accountability Act). All participants signed an informed consent. The study was registered with Clinical Trials.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].

Triple therapy participants with zeaxanthin (TTZ Cohort). This cohort included 64 participants, with a 56% (36/64)/44% (28/64) female/male ratios. The mean participant age was 78.7 years (SD=7.8, 95% CI=76.7-80.7), with a 52-93 year age range. The 64 participants had 72 treated eyes, with 83% (60/72) undergoing a 12-month follow-up exam and 86% (62/72) a 24-month exam. A flow chart (Figure 1) shows participant time interval examinations.

Vision

Twenty-seven percent (17/62) of TTZ Cohort eyes gained ≥ 15 letters (≥ 3-line vision gain) at 24 months, versus 9% (7/81) in the TT Cohort (p=0.006) (Table 3). A 24-month loss of ≥ 15 letters was observed in 10% (6/62) of TTZ Cohort eyes and 10% (8/81) of TT Cohort eyes (p=0.97). Stable (≤ 5 letter loss) or improved vision at 24 months was noted in 76% (47/62) of TTZ Cohort eyes and 77% (62/81) of TT Cohort eyes (p=0.92).

ETDRS vision was converted to LogMAR vision for statistical analysis. Mean TTZ Cohort vision improved from baseline LogMAR 0.78 (SD=0.61, 95% CI=0.63-0.93), or ETDRS 20/125+1, to LogMAR

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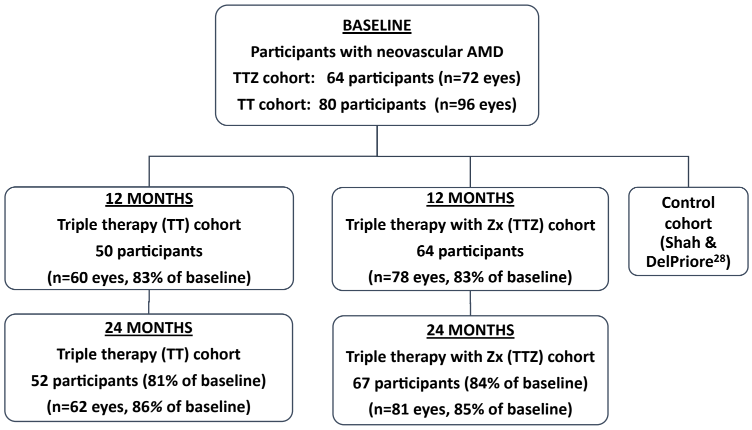

Figure 1: Participant Flow at Various Time Intervals (TT=Triple Therapy; TTZ=Triple Therapy with Oral Zeaxanthin Supplementation; Zx=Zeaxanthin).

Vision Parameter	TTZ cohort	TT cohort	p-value
Gain of ≥ 3 ETDRS lines	27% (17/62)	9% (7/81)	0.006
Loss of ≥ 3 ETDRS lines	10% (6/62)	10% (8/81)	0.97
Stable* or improved vision	76% (47/62)	77% (62/81)	0.92
Vision gain from therapy	20/125^{+1} to 20/63^{-2}	20/100^{-1} to 20/80	0.39

Table 3: Mean Visual Function Parameters at 24 months after baseline. (TTZ=Triple Therapy with Zeaxanthin; TT=Triple Therapy; ETDRS=Early Treatment Diabetic Retinopathy Study; *Stable vision=vision within 5 ETDRS letters of baseline).

0.55 (SD=0.37, 95% CI=0.45-0.65), or 20/63-2, at 24 months (Table 2), a mean 12 EDTRS letter gain (p=0.02). The mean number of treatment cycles was 2.4 (SD=1.5, 95% CI=2.0-2.8) over two years. Mean baseline CNV size was 2.4 disc areas (SD=1.1, 95% CI=2.1-2.7).

In TT Cohort eyes, mean vision improved from LogMAR 0.68 (SD=0.53, 95% CI=0.55-1.0), or 20/100+1, to LogMAR 0.60 (SD=0.34, 95% CI=0.26-0.42), or 20/80, at 24 months (Table 2), a mean gain of 4 ETDRS letters (p=0.24 for baseline *vs.* 2 years) (p=0.50 *vs.* Cohort TTZ). Mean baseline CNV size was 2.3 disc areas (SD=1.1, 95% CI=2.0-2.6) (p=0.86 *vs.* Cohort TTZ).

A comparison of TTZ and TT Cohort visions with those from the historical Control Cohort, 28 is shown in Table 2. There was no significant difference (p=0.39) between the mean baseline visions of 0.78 in the TTZ Cohort and 0.68 in the TT Cohort. A comparison of the mean two-year visions of 0.55 (ETDRS 20/63-2) in the TTZ Cohort and 0.60 (ETDRS 20/80) in the TT Cohort revealed no significant difference (p=0.50).

The mean number of TT Cohort treatment cycles was 2.9 (SD=2.2, 95% CI=2.4-3.4) (p=0.16 *vs.* Cohort TTZ), 21% greater in the TT Cohort than TTZ Cohort.

Contrast sensitivity (Table 4) revealed was no significant difference between the TTZ Cohort and TT Cohort baselines and 24-month results or baseline and 24-month results in the TTZ versus TT Cohort.

Retinal thickness

The TTZ Cohort, baseline, mean central retinal thickness was 305 mμ (SD=82, 95% CI=286-324), and in the TT Cohort was 314 mμ (SD=82, 95% CI=297-331) (p=0.58) (Table 5). At 24 months, the TTZ Cohort had a central macular thickness of 295 mμ (SD=93, 95% CI=269-319), while in the TT Cohort it was 269 mμ (SD=71, 95% CI=252-284) (p=0.09). TTZ Cohort eyes had a mean thickness

Cohort	Baseline contrast sensitivity	24-month contrast sensitivity	p-value
TTZ	0.89	0.84	0.60
TT	0.93	0.88	0.66
p-value	0.63	0.55	

Table 4: Ridgevue Contrast Sensitivity in the TT and TTZ Cohorts. (TTZ=Triple Therapy with Zeaxanthin; TT=Triple Therapy).

Cohort	Central thickness at baseline (mμ)	Central thickness at 24 months (mμ)	p-value
TTZ	305	295	0.57
TT	314	269	0.0003
p-value	0.58	0.09	

Table 5: Retinal Thickness in the Central Macula in Cohorts TTZ and TT. (TTZ=Triple Therapy with Zeaxanthin; TT=Triple Therapy).

Cohort	Conversions in fellow eyes to NVAMD during the current study	Conversions in fellow eyes to NVAMD-Barbazetto et al. [40]	p-value
TT cohort	12/53 (23%)	151/445 (34%)	0.10
TTZ cohort	3/47 (6%)	151/445 (34%)	<0.001*
p-value	0.02*	NA	

Table 6: Choroidal Neovascularization in the Fellow Eye Developing by 24 Months after Baseline Versus Barbazetto et al. [40]. ((Fisher's Exact Test)* (TT=Triple Therapy, TTZ=Triple Therapy with Zeaxanthin, CFT=Central Foveolar Thickness; NVAMD=Neovascular Age-Related Macular Degeneration; NA=Not Applicable)

reduction of 11 microns (3.6%) (p=0.57) versus 46 microns (14.6%) in TT Cohort eyes (p=0.0003).

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 TT Cohort fellow eyes was 23% (12/53) versus 6% (3/47) in the TTZ 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

Model	TTZ cohort	TT cohort	Control Cohort[28]
Combined-eye model (weighted)	7.380	7.180	6.433
QALY and (Percent Patient Value) Gains Associated with Comparisons to No Therapy (Control Cohort) and Between Cohort TTZ vs. Cohort TT			
Model	TTZ Cohort vs. Control Cohort	TT Cohort vs. Control Cohort	Cohort TTZ vs. Cohort TT
Combined-eye model (weighted)	0.947 (14.7%)	0.747 (11.6%)	0.200 (2.8%)

Table 7: QALY (quality-adjusted life-year) Accrual Associated with the Three Cohorts Over 11 Years (discounted at 3% annually), Including Adverse Events. (TTZ=Triple Therapy with Zeaxanthin; TT=Triple Therapy; QALY=Quality-Adjusted Life-Year).

Model	TT cohort	TTZ Cohort
Combined-eye model 11-year cost	$14,480	$14,486
Combined-eye model 2-year cost	$11,092*	$12,882**

Table 8: Model Costs (TT=Triple Therapy; TTZ=Triple Therapy with Zeaxanthin, *=no extra costs of fellow eye conversion to Neovascular Age-Related Macular Degeneration included after two years, **=Zeaxanthin use for only two years).

Incremental Cost-Utility Ratios			
Model	Cost	QALY gain	$/QALY (CUR)
BASE CASE Cohort TTZ vs. Cohort TT using 3-line gains in vision	6	0.144	42
BASE CASE Cohort TTZ vs. Cohort TT using mean visions	6	0.200	30
Average Cost-Utility Ratios			
Combined-eye Model, 11-year cost for Cohort TTZ	$14,486	0.947	$15,296
Combined-eye Model, 11-year cost for Cohort TT	$14,480	0.747	$19,382

Table 9: Cost-Utility Ratios, Combined-Eye Model, 11-Year Time Frame (TT=Triple Therapy; TTZ=Triple Therapy with Zeaxanthin; QALY=Quality-Adjusted Light-Year; $/QALY=Dollars Expended per QALY Gained, CUR=Cost-Utility Ratio).

Model – 11 years unless otherwise indicated	Incremental cost of Cohort TTZ over Cohort TT	Incremental QALY gain of Cohort TTZ over Cohort TT	Incremental $/QALY gain of Cohort TTZ over Cohort TT
Input changes			
Eleven-Year Base Case Zx oral supplement daily for 11 years in Cohort TTZ *vs.* Cohort TT	$6	0.200	$30
Zx oral supplement daily for 2 years only in Cohort TTZ	-$2,715	0.200	-$13,575
Double the cost of zeaxanthin	$3,437	0.200	$17,187
Triple the cost of zeaxanthin	$6,868	0.200	$34,342
Quadruple the cost of zeaxanthin	$10,299	0.200	$51,497
Loss of Zx benefit to decrease fellow eye CNV after year 2, with 11 years of Zx therapy in Cohort TTZ	$2,665	0.041	$65,291
Loss of total Zx benefit after year 2, with 11 years of Zx therapy in Cohort TTZ	$2,665	0.020	$133,346
Loss of total Zx benefit after year 2, with 2 years of Zx therapy in Cohort TTZ	-$57	0.020	-$2,835
Halving the incremental Zx benefit over no Zx	$6	0.100	$60
One additional treatment cycle/year: bevacizumab, PDT &dexamethasone, years 3-11 in both cohorts	$6	0.200	$30
Two additional treatment cycles/year: bevacizumab, PDT &dexamethasone, years 3-11 in both cohorts	$6	0.200	$30
Two-Year Base Case 2-year model with Zx supplementation in Cohort TTZ for 2 years	($1,790)	0.007	-$255,689
Upper limits of cost-effectiveness: 11-year model			
Model	Zeaxanthin cost	QALY gain	Incremental $/QALY
Base case, 11-year, combined-eye model, Zx *cost/year* for cost-utility ratio of $50,000/QALY	$13,426	0.200	$50,000
Base case, 11-year, combined-eye model, Zx *cost/week* for cost-utility ratio of $50,000/QALY	$258	0.200	$50,000
Base case, 11-year, combined-eye model, Zx *cost/day* for cost-utility ratio of $50,000/QALY	$37	0.200	$50,000
Base case, 11-year, combined-eye model, Zx *cost/year* for cost-utility ratio of $55,800/QALY*	$14,586	0.200	$55,800
Base case, 11-year, combined-eye model, Zx *cost/week* for cost-utility ratio of $55,800/QALY*	$281	0.200	$55,800
Base case, 11-year, combined-eye model, Zx *cost/day* for cost-utility ratio of $55,800/QALY*	$40	0.200	$55,800
Base case, 11-year, combined-eye model, Zx *cost/year* for cost-utility ratio of $100,000/QALY	$23,426	0.200	$100,000
Base case, 11-year, combined-eye model, Zx *cost/week* for cost-utility ratio of $100,000/QALY	$451	0.200	$100,000
Base case, 11-year, combined-eye model, Zx *cost/day* for cost-utility ratio of $100,000/QALY	$64	0.200	$100,000
Base case, 11-year, combined-eye model, Zx *cost/year* for cost-utility ratio of $167,400/QALY**	$36,906	0.200	$167,400
Base case, 11-year, combined-eye model, Zx *cost/week* for cost-utility ratio of $167,400/QALY**	$710	0.200	$167,400
Base case, 11-year, combined-eye model, Zx *cost/day* for cost-utility ratio of $167,400/QALY**	$101	0.200	$167,400

Table 10: Sensitivity Analysis. Incremental Cost–Utility Ratios of Cohort TTZ *vs.* Cohort TT with the Combined-Eye Model (2016 US Real $). (Zx=Zeaxanthin; QALY=Quality-Adjusted Life-Year; $/QALY=Dollars Expended per QALY Gained; CUR=Cost-Utility Ratio; TTZ=Triple Combination Therapy with Zeaxanthin/Lutein Cohort, TT=Triple Combination Therapy Cohort; CNV=Choroidal Neovascularization; WHO=World Health Organization). A negative cost-utility ratio indicates that neovascular age-related macular degeneration triple therapy with zeaxanthin dominates triple therapy without zeaxanthin, since it provides greater patient value than triple therapy without zeaxanthin and is also less expensive than triple therapy without zeaxanthin) (Dollars are 2016 U.S. real dollars discounted at 3%/year. QALYs are discounted at 3%/year.). *The World Health Organization upper limit for very cost-effective is 1x Gross Domestic Product per capita, or (1 × $55,800=) U.S. 2015 $55,800 [41,42].**The World Health Organization upper limit for cost-effectiveness is 3x Gross Domestic Product per capita, or (3 × $55,800=) U.S. 2015 $167,400 [41,42].

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 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 ($14,480) 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.

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