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ORIGINAL RESEARCH

Prevention Surpasses Treatment: 5-year Follow-Up, Cost-Utility, and Cost–Benefit of Zeaxanthin Therapy for Neovascular Age-Related Macular Degeneration

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ABSTRACT

Introduction: Oral administration of zeaxanthin (Zx) 20 mg daily in patients with unilateral neovascular age-related macular degeneration (nAMD) treated with triple therapy (photodynamic therapy/intravitreal bevacizumab/intravitreal dexamethasone) reduced fellow-eye 2-year nAMD incidence from 23 to 6% ($p = 0.02$) in a prior clinical trial. We questioned the long-term benefit and thus analyzed case–control 5-year patient data of trial participants and additional participants with 5-year follow-up, also performing cost-utility and cost–benefit analyses.

Methods: Consecutive, unilateral nAMD patient outcomes for those taking 20 mg Zx supplementation orally for ≥ 5 years were compared with the Comparison of AMD Treatments Trials (CATT) 5-year historical controls for fellow-eye nAMD conversion. Eleven-year mean life expectancy, cost-utility and cost–benefit models were undertaken employing a 3% discount rate and 2020 US real dollars.

Results: Among 227 consecutive patients with nAMD/Zx-supplementation, 202 (90%) had 5-year follow-up. The fellow-eye nAMD 5-year conversion incidence using a Kaplan–Meier cumulative event estimate was 22% (49/227), versus 48% (167/348) with CATT control data ($p < 0.0001$). An 11-year cost-utility model with estimates for years 6–11 demonstrated a 0.42 (7.7%) QALY (quality-adjusted life-year) gain, including 3 months of life saved per patient due to decreased nAMD fellow-eye conversion. This yielded a direct ophthalmic medical cost perspective, incremental cost-utility ratio (CUR) of −$576/QALY and a societal cost perspective CUR of −$125,071/QALY. Zx supplementation for all 2020 US unilateral nAMD cases would have theoretically saved society, primarily

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patients, $6.0 billion over 11 years, a 1531% return on investment (ROI), or 31.3% annual ROI, on Zx costs.
Conclusions: Oral zeaxanthin supplementation for unilateral nAMD patients appears to decrease fellow-eye long-term incidence and is cost-effective and financially rewarding. It is dominant vs. no supplementation in patients presenting with unilateral nAMD.
Trial Registration: ClinicalTrials.gov identifier, NCT01527435.

Keywords: Cost-effective; Decreased neovascular macular degeneration; Oral supplementation; Zeaxanthin

Key Summary Points

A published 2-year randomized clinical trial previously revealed that oral zeaxanthin supplementation for patients with unilateral neovascular age-related macular degeneration (nAMD) reduced fellow-eye disease by 75%. Five-year case–control follow-up data herein revealed that zeaxanthin supplementation reduces atrophic fellow-eye conversion to nAMD from 48 to 22%, a 54% decrease.

Zeaxanthin supplementation in patients with unilateral nAMD treated with triple therapy resulted in improved overall vision by preventing conversion of second eyes with atrophic macular degeneration to nAMD. Nonetheless, aside from the diminution of fellow eye conversion to nAMD in unilateral nAMD cases treated with zeaxanthin, there was no difference in vision between the groups with and without zeaxanthin supplementation.

Cost–benefit analysis suggests that oral zeaxanthin supplementation in a 1-year cohort of all 114,000 unilateral US nAMD cases would net patients, insurers, and the American public a discounted US$ 6.0 billion above the cost of zeaxanthin over 11 years, a 1531% return on investment.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of legal blindness in the United States, with neovascular age-related macular degeneration (nAMD) accounting for 90% of such cases [1]. Currently, intravitreal anti-VEGF (vascular endothelial growth factor-inhibitor) monotherapy is a mainstay of nAMD therapy [1, 2], though combination therapy [anti-VEGF monotherapy, corticosteroid, and photodynamic therapy (PDT)] can reduce patient treatment burden [1–6]. Combination therapy vision outcomes are typically similar to anti-VEGF monotherapy outcomes [2–4].

Antioxidants and other supplements have been recommended to prevent advanced dry AMD and nAMD [7–14], with retinal carotenoids zeaxanthin (Zx) and lutein utilized in combination. Zeaxanthin, the predominant carotenoid, is most concentrated in the macula [7–10]. It has been shown to prevent AMD in mice [7] and inhibit VEGF secretion by hypoxic retinal pigment epithelial cells in vitro [8]. Increased dietary carotenoids have been associated with decreased AMD [10] and nAMD [7] in humans, with the POLA (Pathologies Oculaires Liées à l'Age) Study Group [11] reporting that high plasma Zx and lutein levels were associated with a 93% decreased AMD risk versus low levels. Gale et al. [12] found that early and late AMD risk was higher with low plasma Zx levels.

In a non-randomized clinical trial of 424 nAMD participants, Olk et al. [5] noted that oral Zx supplementation to triple therapy reduced 2-year nAMD incidence in AMD fellow eyes from 12.5 to 6.25% ($p = 0.03$). In a subsequent 2-year, 144 nAMD-participant randomized clinical trial, Olk et al. [6] found that in patients with unilateral nAMD receiving no Zx supplementation, 23.0% of fellow eyes developed nAMD, while in participants receiving Zx supplementation, the conversion rate decreased by 75% to 5.8% ($p = 0.02$). Oral Zx supplementation with triple therapy was dominant vs. triple therapy alone, meaning it conferred a greater gain in quality-adjusted life-years (QALY) for less cost than triple therapy alone due to decreased fellow-eye nAMD conversion [6].

When decreased fellow eye conversions to nAMD in the zeaxanthin treated cohort were not considered, however, there was no difference in mean 2-year vision between the cohorts receiving Zx supplementation and receiving triple therapy alone ($p = 0.50$) [6].

Since prior studies have suggested that oral administration of Zx prevents nAMD [5–7, 9], we analyzed 5-year data of treatment with Zx supplementation to assess the unilateral nAMD conversion rate to bilateral nAMD and compare the conversion rate to historical controls not treated with Zx. Employing these data, we then considered an incremental cost-utility analysis (CUA) and cost–benefit analysis of Zx supplementation in cases with baseline unilateral nAMD.

The primary study outcome was fellow eye nAMD to assess if decreased nAMD conversion associated with oral supplementation of zeaxanthin at 2 years persisted with supplementation at 5 years. If it persisted, a cost-utility analysis would be undertaken to evaluate the cost-effectiveness of the supplementation. The secondary outcomes were (1) vision to assess if there was a 5-year vision difference between the cohorts with and without zeaxanthin supplementation who developed nAMD, and (2) a cost–benefit analysis to ascertain the cost of zeaxanthin supplementation versus the funds returned to society from the intervention.

METHODS

Initial Analysis

An initial analysis was undertaken of 340 consecutive baseline participants from the practice of R. Joseph Olk, MD, in St. Louis, Missouri, enrolled between May 2012 and December 2015, with 5-year follow-up, who agreed to take supplemental Zx with triple therapy for presenting nAMD. Of the 340 patients, 227 (67%) had unilateral nAMD, while 113 had bilateral involvement. Three bilateral nAMD patients were excluded for non-compliance (taking less than 75% of Zx doses). Analyses were thus performed on 337 patients, with the primary cohort of interest consisting of the 227 participants who presented with baseline unilateral nAMD.

Demographics

Among the 337 participants enrolled at baseline, 205 (60.8%) were women and 132 (39.2%) were men. The median age was 80 years, and the mean age was 79.3 years (standard deviation [SD] = 8.8, 95% confidence interval [CI] = 78.3–80.1), ranging from 42–98 years.

In the 227-participant unilateral cohort, the baseline age was 79 years [SD = 8; 95% CI 78–80], with an 80-year median and range of 58–98 years. Women comprised 61% (138/227) and men 39% (89/227).

Inclusion Criteria

In our economic analyses we included consecutive participants with unilateral classic, minimally classic and/or occult nAMD who took 20 mg Zx orally each day in conjunction with triple therapy after careful explanation. Macular blood, subretinal fluid, subretinal pigment epithelial fluid, and/or hard exudate were typically present. Optical coherence tomography (OCT) confirmed the presence of subretinal fluid, subretinal pigment epithelial fluid and retinal edema. The presence of choroidal neovascularization was confirmed by intravenous fluorescein angiography and/or indocyanine green (ICG) angiography.

Exclusion Criteria

Eyes with fibrotic nAMD were excluded, as were those with choroidal neovascularization exceeding 12 disc areas. Blood was not an exclusion criterion unless it covered > 12 disc areas [4, 5]. Patients with no posterior segment drusen in either eye were excluded.

Triple Therapy/Zx Treatment Cohort

All eyes with nAMD were treated with the regimen shown in Tables S1 and S2. One treatment cycle consisted of (1) fundus photographs,

fluorescein angiography/indocyanine green angiography, (2) a 1.25-mg intravitreal injection of bevacizumab at baseline, 1 month, 2 months and 3 months, (3) a 1.0 mg intravitreal dexamethasone injection at baseline, (4) 40 mg of sub-Tenon's methylprednisolone acetate within 1 week, and (5) reduced-fluence photodynamic therapy (PDT) within 2 weeks utilizing verteporfin (6 mg/m^2 × body surface area in meters squared) given intravenously over 10 minutes, followed by a 689-nm wavelength light dose of 25 J/cm^2 for 83 seconds. Optical coherence tomography was performed at the beginning and end of each treatment cycle.

Patients were re-examined at 4–6 weeks after each treatment cycle, and Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity was measured at every visit. If considered stable, patients were followed every 2 months for 6 months, and then every 3 months thereafter. Another 3-month cycle of triple therapy was administered when retreatment was indicated. Retreatment was predicated on the occurrence of subretinal blood, subretinal/intraretinal fluid on OCT, decreased vision, fluorescein angiographic leakage, or an occult plaque seen with ICG angiography.

The incidence of participants requiring topical anti-hypertensive therapy for increased intraocular pressure secondary to corticosteroid therapy with triple therapy was approximately 2%. No participant required glaucoma surgery. Five percent of patients developed cataracts in eyes treated with triple therapy attributable to the corticosteroid therapy over the 5-year period.

Oral Supplementation

Among all 337 nAMD patients presenting, (85/337 =) 25.2% took an AREDS oral supplement (PreserVision; Bausch & Lomb, Laval, Quebec, Canada), while all patients took AREDS2 supplements containing 2 mg Zx and 10 mg lutein after May 2013, throughout 5 years and beyond. Each patient was also placed on 20 mg of orally administered zeaxanthin (EyePromise, Chesterfield, MO) daily from baseline through at least 5 years. Patients were questioned about Zx usage at each visit, and its importance was emphasized. Pill counts were undertaken at 3 months, 6 months, 12 months, and 24 months.

Among all 337 nAMD participants, the 25.8% (87/337) presenting prior to May 2013 took a daily AREDS oral supplement (PreserVision; Bausch & Lomb, Rochester, NY, USA) which did not contain zeaxanthin or lutein for an average of 2.5 months, while all patients took a daily AREDS2 supplement containing 2 mg Zx and 10 mg lutein (PreserVision AREDS2; Bausch & Lomb, Rochester, NY, USA) from May 2013 forward, through 5 years and beyond. Thus, among all 337 patients in the study, 25.2% took AREDS supplements for 4.2% (2.5 months/60 months) of their 5-year study time and AREDS2 supplements for 95.8% of their 5-year study time. The remaining 74.8% of participants recruited from May 2013 forward took AREDS2 supplements for 100% of their 5-year study time. Thus, overall, participants on average took AREDS supplements for 1.06% of the study time and AREDS2 supplements for 98.94%.

Cost-Utility Analysis for Participants Presenting with Unilateral nAMD

A CUA was performed utilizing a Value-Based Medicine® (standardized) model with patient utilities [1, 15–17] and recommendations of the Second Panel on Cost-effectiveness in Health and Medicine [18] in conjunction with CHEERS criteria. The model features are listed in Table 1 [16–28].

Overview

The model compared the 5-year nAMD conversion incidence in fellow eyes treated with oral Zx supplementation versus historical controls not using Zx in an extrapolated 11-year (mean life expectancy of a patient presenting with unilateral nAMD [1, 28]) incremental cost-utility analysis. The analyses used a $/QALY (dollars expended per quality-adjusted life-year gained) outcome, the cost-utility ratio (CUR). This analysis included 227 consecutive patients with unilateral nAMD and atrophic AMD in the

Table 1 Input parameters utilized in the cost-utility analysis

Parameter	Variant	Source
Time trade-off utilities	Vision utilities, validated [19], reliable [20, 21]	Patients with ophthalmic diseases [19–26]
Costs	Average national costs in 2020 real US $	2020 Medicare Fee Schedule [27]
Annual discount rate = 3%	For QALY (quality-adjusted life-year) outcomes and costs	Second Panel on Cost-Effectiveness in Health and Medicine [18]
Cost perspectives	Both health (ophthalmic) and societal	CVBM [1, 15] and Second Panel on Cost-Effectiveness in Health and Medicine [18]
Time frame	11 years [28]	Baseline life expectancy of nAMD patient
Eye models	Combined-eye model (weighted 1-eye and 2-eye models)	CVBM methodology per patient preferences [1, 15]
Outcomes	Cost-utility analysis in $/QALY, or $ expended per QALY gained, and ROI	CVBM [1, 15] and Second Panel on Cost-Effectiveness in Health and Medicine [18]
Analysis	Incremental CUA in unilateral nAMD cases for oral supplementation of Zx vs. none	Outcome = development of nAMD in fellow eye with atrophic AMD

TTO time trade-off, *QALY* quality-adjusted life-year, *nAMD* neovascular age-related macular degeneration, *$/QALY* dollars expended per quality-adjusted life-year gained, *CUA* cost-utility analysis, *Zx* oral zeaxanthin, *CVBM* Center for Value-Based Medicine®, *ROI* financial return on investment

fellow eye. Atrophic fellow-eye conversion data from the Comparison of AMD Treatments Trials (CATT) [29, 30], a randomized clinical trial comparing the 5-year effects of ranibizumab and bevacizumab for the treatment of nAMD were used as comparators for nAMD fellow-eye conversion rates. Macular Photocoagulation Study Group data were also compared [31].

Patient, time trade-off, vision utilities, the 2020 non-facility, national average Medicare Fee Schedule [27] (Table S4) both health (direct ophthalmic medical) and societal cost perspectives, and a commonly employed 3%/year discount rate for QALYs and costs were used [18].

Utilities

Time trade-off vision utilities were acquired by direct interview from over 1400 ophthalmic patients to quantify the quality of life associated with vision in the better-seeing eye [19–26]. The utilities have excellent validity [19] and reliability [20, 21] and are typically unaffected by age, gender, ethnicity, level of education, underlying ophthalmic disease, and systemic comorbidities [19–26].

Time Frame

The duration of Zx therapy was 5 years. Table S5 shows total follow-up of the cohort receiving Zx over 5 years. Of the 227-baseline unilateral nAMD participants, 5-year follow-up was available for (202/227 =) 88.9%, while among all 337 patients with baseline unilateral or bilateral nAMD, the 5-year follow-up was 90.5% (305/557).

An 11-year cost-utility model was selected since the life expectancy of the average 79-year-old unilateral nAMD patient at baseline was 11 years [1, 28]. The Second Panel on Cost-Effectiveness in Health and Medicine recommends the longest reasonable time frame for a cost-utility analysis to aid with decision making [18]. A last observation carried forward methodology was employed for nAMD fellow-eye conversions from years 6–11 using an average of year 1–5 conversion rates for our cohort

treated with Zx and the CATT control cohort [29]. Triple therapy frequency from years 6–11 assumed patients were seen 3x/year [1, 5, 6]. Optical coherence tomography was obtained at each visit.

Vision outcomes for nAMD with different anti-VEGF monotherapies [1] and multi-therapies [1–4] have been shown to be similar [1–4]. In addition, because our prior 2-year randomized trial [6] demonstrated similar visual outcomes in nAMD eyes receiving triple therapy and triple therapy with Zx supplementation, we assumed that Zx supplementation had no acute intrinsic effect upon individually treated nAMD vision. Instead, supplementation with Zx reduced atrophic AMD fellow-eye conversion in eyes with mean 20/40 mean to nAMD, thereby improving the mean vision overall for the cohort receiving Zx supplementation.

Direct Ophthalmic Medical Costs

Unless otherwise specified, costs were in 2020 US real dollars. For the 227 unilateral nAMD cases, we also accrued the Zx cost to second-eye treatment costs needed over the 5-year period. In essence, the costs of triple therapy + Zx supplementation for second-eye conversion to nAMD were compared to the cost of triple therapy alone for second-eye conversion to nAMD in our control cohort not treated with Zx. Direct ophthalmic medical costs did not include medical costs associated with extra time of life gained from Zx supplementation, though the societal costs did.

Societal Costs

These included direct ophthalmic medical costs, direct non-ophthalmic medical costs [27, 32, 33], direct non-medical costs [34, 35] and indirect medical costs [35–38]. The societal costs saved by decreased second-eye nAMD conversion were measured by comparing the economic loss associated with the resultant mean second-eye vision in the cohorts receiving treatment with and without Zx supplementation annually over 11 years in unilateral nAMD cases [32–38].

Direct Non-Ophthalmic Medical Costs

These vision loss-related costs, including those for depression, injury, facilities, Medicare, and nursing homes [32], were converted to 2020 real dollars utilizing the Consumer Price Index (CPI) for medical care [33]. Direct non-medical costs, or caregiver costs, included those for inside and outside activities of daily living, residence change and transportation [34, 35], while indirect medical costs encompassed primarily wage loss due to decreased vision [35–38]. The latter two category costs were adjusted to 2020 real US dollars using the CPI [35]. In addition, the medical costs incurred due to years of life saved from Zx supplementation were incorporated [1].

The net societal costs saved over and above the direct ophthalmic medical costs and medical costs incurred by extending life were accrued as negative costs against the Zx costs to obtain the 11-year Zx return on investment (ROI).

Statistics

The cumulative incidence of 5-year fellow-eye conversion to nAMD was calculated employing Kaplan–Meier product-limit method estimates [39]. The chi-square test compared categorical variables such as proportions with fellow eye progression to nAMD. Linear variables, such as vision, were compared using the t-test (Microsoft, Bellevue, WA, USA). Significance was presumed to occur at $p < 0.05$.

Sample Size

By employing prior data [5, 6] and two-sided equality, sample size analysis to compare nAMD conversion proportions in the cohort receiving triple therapy with Zx supplementation and historical controls not receiving Zx revealed that 85 participants in each unilateral nAMD sample were required for 90% power to detect a significant difference at $p < 0.05$ [40]. The numbers utilized were based primarily upon a previous 2-year clinical trial [6] in which 3 of 47 (6%) patients with atrophic AMD fellow eyes undergoing 20 mg daily oral zeaxanthin supplementation converted to nAMD, versus 12 of 53 (23%) patients with atrophic AMD fellow eyes in a cohort not receiving supplementation ($p = 0.03$; Fisher exact test).

Table 2 Mean vision in fellow eyes of baseline unilateral nAMD participants treated in nAMD-converted fellow eyes with triple therapy with zeaxanthin versus VEGF-I monotherapy without zeaxanthin, the latter rate as in CATT [29, 30]

	Cohort treated with Zx (triple therapy)	Cohort not treated with Zx (CATT) [29, 30] (VEGF-I monotherapy)
Year	Vision (fellow eyes converted)	Vision (fellow eyes converted)
Baseline	20/40 (0%)	20/40 (0%)
1	20/43 (9%)	20/44 (8%)
2	20/46 (17%)	20/49 (20%)
3	20/49 (21%)	20/53 (29%)
4	20/49 (21%)	20/60 (39%)
5	20/50 (22%)	20/68 (48%)
6	20/52 (26%)	20/76 (53%)
7	20/55 (30%)	20/86 (58%)
8	20/58 (33%)	20/100 (62%)
9	20/60 (36%)	20/105 (65%)
10	20/63 (39%)	20/110 (69%)
11	20/65 (41%)	20/125 (72%)
Age (baseline)	79 years	78 years
Age (range)	58–98 years	59–92 years
Baseline #	227	727
Gender (M/F)	61%/39%	65%/35%
5-year follow-up	90% (202/227)	49% (348/727)
Caucasian	98.5%	98.2%
Enrollment	2012–2015	2008–2009
AREDS2 [23, 63, 64]	100% (99% AREDS2)	67% (90% if other supplements included [63, 64])

conv. conversion, *Zx* zeaxanthin, *CATT* Comparison of AMD Treatment Trials [29], *nAMD* neovascular age-related macular degeneration

Institutional Review Board (IRB) Approval

All subjects gave written informed consent for inclusion before participation. The Wills Eye Hospital IRB approved utility acquisition, and the study adhered to the Declaration of Helsinki and its amendments. The SSM Health Care Institutional Review Board approved triple therapy with Zx supplementation (approval number 14-07-0540). The ClinicalTrials.gov identifier for the original randomized clinical trial is NCT 01527435 [6].

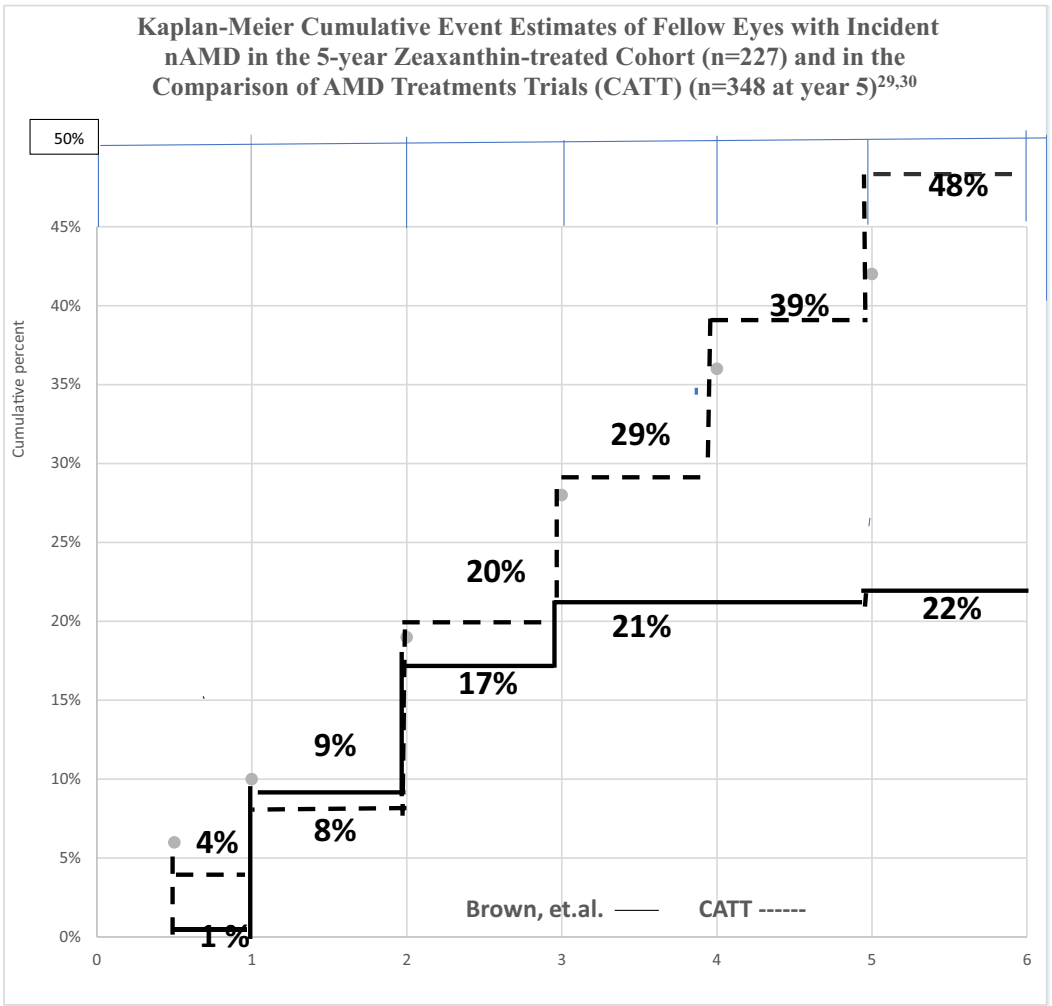

Fig. 1 Kaplan–Meier cumulative event estimates of fellow eyes with incident nAMD in the cohort treated with zeaxanthin over a 5-year period (n = 227) and in the CATT (n = 348 at year 5). Events = fellow eyes converting to nAMD (neovascular age-related macular degeneration). Censored = number of patients who died or were lost to follow-up

RESULTS

Clinical Data

The mean baseline vision in nAMD eyes in the complete 337-person unilateral and bilateral nAMD was 20/125, while at 5 years it was 20/160. Baseline nAMD vision in the CATT cohort treated with VEGF monotherapy was 20/63+2 and 5-year mean vision was 20/63–1 [2]. Shah and DelPriore [41], utilizing untreated Macular Photocoagulation Study cohort data,

Table 3 Comparison of the development of nAMD in fellow eyes relative to historical control cohorts without Zx supplementation

Study	Baseline fellow eyes at risk	nAMD conversion (%)	*p*-value vs. current study
Current study	227	1-year: 9% (20/227)	NA
		2-year: 17% (38/227)	
		3-year: 21% (48/227)	
		4-year: 21% (48/227)	
		5-year: 22% (49/227)	
CATT [29, 30]	661	2-year: 20% (123/620)	0.08
		5-year: 48% (167/348)	< 0.0001
Macular Photocoagulation Study [31]	670	5-year: 42% (281/670)	< 0.0001
United Kingdom Age-Related Macular Degeneration Electronic Medical Records Users Group [42]	11,135	3-year: 42% (4677/11,135)	< 0.0001
Moorfields AMD Database [43]	2300	2-year: 32% (742/2300)	< 0.0001
Starr et al. [44]	22,553	3-year: 29% (6471/22,553)	0.001
Barbazetto et al. [45]	445	2-year: 36% (161/445)	< 0.0001
Parikh et al. [46]	1561	2-year: 24% (375/1561)	0.01
Three Continent Study [47]	92	5-year: 44% (42/96)	< 0.0001

nAMD neovascular age-related macular degeneration, *Zx* zeaxanthin, *NA* not applicable, *CATT* Comparison of Age-Related Macular Degeneration Treatments Trial

performed a Lineweaver-Burk meta-analysis demonstrating that mean vision in the untreated nAMD cohort decreased with increasing duration of nAMD. In addition, Boyer et al. [42] demonstrated that nAMD patients treated sooner with VEGF inhibitors had better vision outcomes. Thus, we did not have a comparable historical 5-year control cohort to demonstrate a 5-year vision benefit in treated nAMD eyes between our participants with nAMD receiving Zx supplementation and the CATT nAMD participants who did not receive Zx supplementation. We therefore confined our major clinical and economic analyses to nAMD fellow-eye conversions in our nAMD participants who received Zx supplementation and the CATT nAMD participants [2, 29, 30] who did not receive Zx supplementation.

Vision

Mean baseline visual acuity in the atrophic AMD fellow eyes of the 227-participant cohort presenting with unilateral nAMD was 20/40 (Table 2). This mean vision remained 20/40 at 5 years in fellow eyes if no nAMD conversion occurred and was assumed to remain so through the 11-year model. The mean vision in the fellow eyes developing nAMD in the cohorts

Table 4 Overall cost per presenting eye completing 11-year treatment (2020 US real dollars discounted at 3% annually)

Year	No. Tx cycles	Consultation	Tx cycles ($3301/cycle)	Office visits	Fundus photos, IVFA/ICG angiography	OCT	Zeaxanthin	Adverse events	Total
1	1.56	153	5150	270	570	125	360	3	6631
2	0.56	0	1731	262	189	121	350	1	2654
3	0.29	0	902	255	99	117	339	1	1713
4	0.24	0	725	247	79	114	329	1	1495
5	0.18	0	528	280	58	129	320	1	1316
6	0.06	0	171	306	19	141	311	1	949
7	0.06	0	166	297	18	137	301	0	919
8	0.06	0	161	288	18	133	293	0	893
9	0.06	0	156	280	17	129	284	0	866
10	0.06	0	152	272	17	125	276	0	842
11	0.06	0	147	264	16	122	268	0	817
Total	3.17	153	9989	3021	1100	1393	3431	8	19,095
Total without Zx	3.17	153	9989	3021	1100	1393	0	8	15,664

Tx treatment, *IVFA* intravenous fluorescein angiography, *ICG* indocyanine green, *OCT* optical coherence tomography, *nAMD* neovascular age-related macular degeneration, *Zx* zeaxanthin

receiving and not receiving Zx supplementation decreased over 11 years as the 20/40 atrophic AMD fellow eyes in each sub-cohort converted to the same 20/125–20/160 vision level associated with nAMD triple therapy. Since the atrophic AMD fellow-eye conversion rate to nAMD was greater in eyes of patients not receiving Zx supplementation, the mean fellow-eye vision in that sub-cohort deteriorated more rapidly.

The median baseline age in the comparator CATT cohort was 78 years (79 years in our cohort) with an age range of 59 to 92 years (58–98 in our cohort). In the CATT cohort, 65% of participants were female, versus 61% in our cohort (Table 2). Among CATT enrollees, 98.5% were Caucasian, while 223/227 (98.2%) in our cohort were Caucasian. CATT participants were enrolled from 2008 through 2009; ours were enrolled from 2012 to 2015.

Conversion Rate of Fellow Eyes to nAMD

The 5-year conversion incidence in our cohort receiving Zx supplementation ($n = 227$) and that in patients in the CATT cohort who did not receive Zx ($n = 348$) [29, 30] are shown in a Kaplan–Meier cumulative event estimate [39] graph in Fig. 1. By 5 years, atrophic fellow eyes had converted to nAMD in 22% of our patients treated with Zx, whereas 48% of atrophic fellow eyes had converted in CATT [29] ($p < 0.001$), making our hazard ratio (22%/48% =) 0.46. The 5-year second-eye nAMD conversion rate in the patients not receiving Zx in the Macular Photocoagulation Study was 42%, and in the Three

Table 5 Second eye, direct ophthalmic medical cost perspective conversion costs of atrophic AMD to nAMD in fellow eye of baseline unilateral nAMD cases

Timeline	Current study conversion A (cum.)	CATT conversion [29] B (cum.)	Tx cost/patient of 2nd eye nAMD when it develops C	Conversion tx cost/patient with current study data D = A × C	Conversion tx cost/patient with CATT data E = B × C	Current study minus CATT conversion costs F = D–E
Year 1	9%	8%	$15,664	$1410	$1253	$157
Year 2	17%	20%	$14,659	$1173	$1759	−$586
Year 3	21%	29%	$13,666	$547	$1230	−$683
Year 4	21%	39%	$12,686	$0	$1269	−$1269
Year 5	22%	48%	$11,716	$117	$1054	−$937
Year 6	26%	53%	$10,757	$430	$538	−$108
Year 7	30%	58%	$9806	$392	$490	−$98
Year 8	33%	62%	$8524	$256	$341	−$85
Year 9	36%	65%	$7110	$213	$213	$0
Year 10	39%	69%	$5529	$166	$221	−$55
Year 11	41%	72%	$3064	$61	$69[a]	−$8
11 years		Total triple therapy costs (11-year)		$4765	$8438	−$3673
11 years		11-year Zx cost		$3431	$0	$3431
11 years		Total mean 11-year cost/patient		$8196	$8438	−$242

CATT Comparison of AMD Treatments Trials, *nAMD* neovascular age-related macular degeneration, *tx* treatment, *Zx* oral zeaxanthin, *CUR* cost-utility ratio, *cum.* cumulative

11 years—Incremental, direct ophthalmic medical cost for second eye nAMD conversion in 114,173 patients with unilateral baseline nAMD: ($198 × 114,173 =) −$27.63 million

[a]NB. Adjusted cost. Without Zx, the mean lifespan of a patient with baseline unilateral nAMD treated in the second eye with triple therapy alone decreases by 0.25 years from 11.0 to 10.75 years. Thus, not receiving Zx supplementation decreases direct ophthalmic medical costs in the cohort not treated with Zx by 25% for both first-eye triple therapy ($559 × −0.25 =) $140 in year 11 and second-eye triple therapy by ($92 × −0.25 =) $23 in year 11

Continent Consortium Report it was 44% (Table 3) [2, 29, 30, 43–48]. The cumulative extrapolated conversion rate in our cohort treated with Zx was 41% at the end of 11 years, while in the CATT cohort it was 72% (Table 2). CATT 5-year data [29] were used in the cost-utility analysis comparing nAMD conversion rates since they were recent, included many patients taking AREDS2 supplements, and involved large numbers of participants. Annual conversion rates for our participants and CATT participants for years 6–11 were calculated using the average of the first 5-year annual percentage conversion rates for each cohort.

Table 6 Societal cost perspective CUR associated with 11-year Zx-supplementation for management of the 2020 US cohort of second eye conversion to nAMD in baseline unilateral nAMD cases

Cost	A = Cohort with Zx supplementation	B = Cohort without Zx supplementation	A − B = Difference (Zx-supplemented minus no Zx treatment)
A. Direct ophthalmic medical expended	+ $8196 (With Zx cost)	+ $8438 (No Zx cost)	−$242
B. Medical costs for 0.25 year saved	+ $10,847	$0	+ $10,847
C. Direct non-ophthalmic med. costs saved	$0	$0 (relative to Zx)	$0
D. Incremental indirect medical (caregiver) costs saved	−$63,135	$0 (vs. cohort treated with Zx)	−$63,135
E. Direct non-medical (wage loss) costs saved	$0	$0 (vs. cohort treated with Zx)	$0
Total costs expended (A + B)	$19,043	$8438	$10,605
Total costs saved (C + D + E)	−$63,135	$0	−$63,135
Net costs saved (sum of A thru E)	−$44,093	$8438	−$52,530
Direct Ophthalmic Medical CUR = −$242/0.42 QALY = −$576/QALY			
Societal CUR = −$52,530/0.42 QALY = −$125,071/QALY			
Societal cost–benefit ratio = NET COST GAIN (114,173 patients × $52,530 = $6.0 billion) divided by UNILATERAL nAMD PATIENT ZX COST (114,173 × $3431 = $391.7 million) = 1531% ROI over 11 years			

CUR cost-utility ratio, Zx oral zeaxanthin, *nAMD* neovascular age-related neovascular macular degeneration, *ROI* return on investment

Incremental Cost-Utility Analysis of 227 Baseline Patients with Unilateral nAMD Undergoing Triple Therapy with Zx Supplementation vs. Triple Therapy Alone

QALY Gain from Zx Supplementation

QALY gain was calculated in the 227-baseline unilateral nAMD cases by comparing the mean vision in fellow eyes of patients receiving Zx and those of patients not receiving Zx in CATT [29]. The major QALY gain occurred because the best-seeing eye utility remained at 0.8, correlating with 20/40 vision [16], in a greater proportion of eyes with Zx supplementation due to a lower incidence of conversion to nAMD in atrophic fellow eyes. The resultant 11-year QALY gain attributable to Zx supplementation, considering the adverse events of one case of endophthalmitis and irritation from the injections, was calculated to be 0.396, a 7.2% QALY gain over the 5.58 QALY accrual in the CATT cohort not treated with Zx. Nonetheless, as shown in Table S4, when the 0.25 year of life was gained as a result of better average vision from Zx supplementation because of decreased AMD conversion to nAMD (See Societal Costs below), another 0.027 QALY was gained for a total QALY gain of (0.396 + 0.027 =) 0.423 QALY. Thus, the quality-of-life component of QALY gain comprised (0.397/0.423 =) 93.7% of the total QALY gain and the length-of-life gain comprised (0.027/0.423 =) 6.3%. No serious adverse ocular or systemic events, including crystalline retinopathy, were noted due to Zx supplementation.

Table 7 Cost-utility sensitivity analysis for nAMD conversion rates in fellow eyes in patients with baseline unilateral nAMD

Direct Ophthalmic Medical Cost Perspective			
Average annual cumulative nAMD conversion rate differences in Zx-treated eyes minus those in non-Zx-treated eyes	**Direct ophthalmic medical cost**	**QALY gain**	**$/QALY**
43.6% (see Table 6) (Base case with CATT data [29])	−$242	0.42	−$576
20%	$1404	0.19	$7389
10%	$1471	0.097	$15,165
5%	$1832	0.048	$38,167
3%	$1977	0.029	$68,172
2%	$2049	0.019	$107,842
1%	$2121	0.01	$212,100
Societal Cost Perspective			
Average annual cumulative nAMD conversion rate differences in Zx-treated eyes minus those in non-Zx-treated eyes	**Societal cost (including all medical costs)**	**QALY gain**	**$/QALY**
43.6% (see Table 6) (Vs. base case CATT data [29])	−$52,530	0.42	−$125,071
20%	−$37,132	0.19	−$195,432
10%	−$12,738	0.097	−$131,320
5%	$1832	0.048	$38,167
3%	$1977	0.029	$68,172
2%	$2049	0.019	$107,842
1%	$2121	0.01	$212,100

nAMD neovascular age-related macular degeneration, *Zx* oral zeaxanthin, *QALY* quality-adjusted life-year, *CATT* comparison of AMD treatment trials [29], *$/QALY* dollars expended per QALY gained

Costs

The 11-year, direct ophthalmic cost for triple therapy with Zx supplementation at baseline for an eye with nAMD in unilateral nAMD cases was $19,095 (Table 4). If a second eye presented with nAMD and the first eye was untreatable, or if both eyes were involved, the 11-year cost of treating the second eye was $15,664 (Table 4), the cost of treating the first eye minus the $3431 cost of Zx supplementation.

Unilateral Baseline nAMD Case, Mean Direct Ophthalmic Medical Costs for Treating Conversion of Atrophic AMD to nAMD in the Fellow Eye

Calculation of the cost differential between atrophic fellow eyes converting to nAMD with and without Zx-supplementation is shown in Table 5. The different triple therapy costs averaged $4765 in the Zx-supplemented cohort, although the 11-year, $3431 Zx cost, assuming all baseline unilateral nAMD participants were

Table 8 Sensitivity analysis of cost–benefit analysis of decreased second-eye nAMD conversion in the Zx-treated cohort (societal cost perspective, 11-year model with 2020 real US$)

Decrease in conversion of fellow eyes to nAMD for the cohort receiving Zx supplementation vs. no Zx supplementation	A. Direct ophthalmic medical costs	B. Systemic medical costs of ¼-yr life gain	C. Non-direct medical caregiver costs	D. Minus costs = costs saved due to less nAMD conversion with Zx supplementation	= D/A 11-year ROI for direct ophthalmic medical costs expended	Annual ROI for direct ophthalmic medical costs
−43.6% (see Table 6) vs. base case CATT data [29])	−$242	$10,847	−$63,135	−$52,530	NC	NC
−20%	$1404	$5424	−$49,383	−$42,555	3031%	36.4%
−10%	$1471	$2712	−$25,056	−$20,873	1419%	27.3%
−5%	$1832	$1356	$0	$3188	−174%	−15.8%
−3%	$1977	$0	$0	$1977	−100%	−9.1%
−2%	$2049	$0	$0	$2049	−100%	−9.1%
−1%	$2121	$0	$0	$2121	−100%	−9.1%

Note that negative values indicate costs saved or dollars returned to society, predominantly patients, while positive values indicate expenditures

Zx oral zeaxanthin, *ROI* financial return on investment, *nAMD* neovascular age-related macular degeneration, *CATT* Comparison of AMD Treatment Trials [29]

NC not calculable since the direct ophthalmic medical costs are negative

supplemented for 11 years, raised the mean ophthalmic treatment costs to $8196. For the non-Zx-treated cohort, the triple therapy costs were $8438, but no Zx costs were accrued. Thus, the mean 11-year, incremental, direct ophthalmic cost for treating second eyes converting to nAMD with triple therapy and Zx-supplementation in baseline unilateral nAMD patients was ($8196–$8438 =) −$242, less than without supplementation with Zx.

Societal Costs

Data from Christ et al. [49] referent to the Salisbury Eye Evaluation Study demonstrated that the incremental decreased vision in the cohort not treated with Zx was associated with a higher risk of premature death, specifically decreasing the life expectancy in this cohort from 11 years to 10.75 years for the average patient.

Premature mortality of a patient who did not receive Zx supplementation [49] also decreases the direct ophthalmic medical cost between years 10.76 and 11 for treating second eyes in the cohort not treated with Zx. This decreased cost totaled $23 and was considered in the direct ophthalmic medical cost perspective CUA (Table 5).

More relevant, the 0.25 years of life saved resulted in extra mean 2020 US real dollar healthcare cost (including nursing home cost) for a 90-year-old patient with baseline unilateral nAMD receiving Zx supplementation of $10,847 [50–52]. This direct non-ophthalmic medical cost was accrued in the cohort receiving Zx supplementation in the societal cost perspective analysis.

The mean 11-year societal costs saved per patient in the baseline unilateral nAMD, Zx-treated cohort by reducing the nAMD conversion incidence of second eyes totaled −$52,530 including the $10,847 11th-year direct non-ophthalmic medical cost addition during 0.25 years of saved life and the −$242 lower direct ophthalmic medical cost in the Zx cohort

Table 9 Mean vision in the 337-participant AMD cohort (baseline unilateral and bilateral nAMD cases) treated with triple therapy with zeaxanthin and an untreated nAMD historical control cohort

Year	Vision in nAMD eyes treated with Zx (utility)	Historical untreated control cohort (utility) [1, 33]
Baseline	20/125 + 1 (0.675)	20/63 (0.74) [1]
	Atrophic AMD fellow eye: 20/40 (0.8)	
1	20/125 + 2 (0.675)	20/125–2 (0.66) [1]
2	20/125 (0.672)	20/200 (0.62) [1]
3	20/125–2 (0.663)	20/250 + 1 (0.612) [41]
4	20/160 + 2 (0.658)	20/250–2 (0.604) [41]
5	20/160 + 1 (0.653)	20/320 (0.596) [41]
6	20/160 + 1 (0.653)	20/400 (0.58) [41]
7	20/160 + 1 (0.653)	20/500 (0.563) [41]
8	20/160 + 1 (0.653)	20/500–2 (0.552) [41]
9	20/160 + 1 (0.653)	20/630 + 1 (0.543) [41]
10	20/160 + 1 (0.653)	20/630 (0.538) [41]
11	20/160 + 1 (0.653)	20/630 (0.538) [41]

ETDRS Early Treatment Diabetic Retinopathy Study, *AMD* age-related macular degeneration, *nAMD* neovascular age-related macular degeneration, *utility* time trade-off utility

(Table 6). The costs were calculated by comparing fellow eye vision in patients receiving Zx supplementation and those not receiving Zx and correlating these with medical costs [27, 32], caregiver costs (transportation, inside and outside activities of daily living and residence change) [34] and wage differences associated with different vision levels [35–37]. No difference in wage costs was noted between our cohort and the CATT cohort at 11 years. There was, however, a caregiver cost gain of $63,135 saved by the average patient treated with Zx over 11 years.

Cost-Utility Ratios

The direct ophthalmic cost-utility ratio for Zx usage in patients with unilateral nAMD was (−$252/0.42 =) −$576/QALY and the societal cost-utility ratio was (−$52,530/0.42 =) −$125,071/QALY. The negative cost-utility ratios with each cost perspective indicate that Zx supplementation was dominant to no supplementation, since Zx supplementation conferred greater QALY (value) gain for less cost in each instance.

Incremental Cost-Utility Sensitivity Analysis on Zeaxanthin-Treated Baseline Unilateral nAMD Cases with Fellow-Eye Conversion

Conversion Rates of Fellow Eyes to nAMD

Considering the nAMD fellow-eye conversion ratio to be the least certain variable, we assessed alternatives shown in Table 7. Employing the direct ophthalmic medical cost perspective for a cost-utility upper limit of $100,000/QALY frequently used in the US [17], the average of nAMD relative, fellow-eye conversion rates over 11 years with Zx supplementation needed to be 2–3% less versus that of patients not treated with Zx. With the societal cost perspective, the $100,000/QALY ceiling was also reached at the 2–3% lower relative conversion rate of nAMD

Table 10 Average CURs for 337-patient cohort treated with triple therapy and baseline unilateral nAMD patients with oral supplementation of Zx versus no nAMD therapy

Baseline model	Percent (%)	Cost 1st-eye	Cost 2nd-eye	Direct medical costs from life gain	Total cost (1st + 2nd eye) in combined-eye model	QALY gain/No tx accrual (%)	$/QALY
Direct ophthalmic medical cost perspective							
1st-eye model	67	$19,095	$242	$0	($19,095 − $242) = $18,853	**0.42**/5.48 = 7.7%	$18,853/0.42 = $44,888/QALY
2nd-eye model	33	$0	$4794	$0	$4794	1.045/5.18 = 21.1%	$4794/1.095 = $4378/QALY
Combined model	100	NA	NA	$0	(0.67 × $19,293) + (0.33 × $4794 = $14,213	0.643/5.28 = 12.2%	$14,213/0.643 = $22,105/QALY
Societal cost perspective							
1st-eye model	67	$19,095	−$63,135–$242 + $10,847 = −$52,530	$10,847	($19,095 − $52,530) = −$33,435	0.42/5.48 = 7.7%	−$33,4350.42 = −$79,607/QALY
2nd-eye model	33	$0	−$188,144 + + $4797 + $43,388 = −$139,959	$43,388	−$139,959	1.045/5.18 = 21.1%	−$139,959/1.045 = −$133,939/QALY
Combined model	100	NA	NA	$21,586	= (0.67 × −$33,435) + (0.33 × −$139,959) = −$68,293	0.643/5.28 = 12.2%	−$68,588/0.643 = −$106,669/QALY

Money returned to society over 11 years from a 1-year new nAMD cohort treated with triple therapy and oral administration of zeaxanthin was therefore (170,400 patients × −$68,293) = $11.78 billion in 2020 US real dollars. This was a ($68,293/$14,213 =) 480% 11-year ROI

CUR cost-utility ratio, *QALY* quality-adjusted life-year, *$/QALY* dollars expended per quality-adjusted life-year gained (the cost-utility ratio), *Zx* oral zeaxanthin, *nAMD* age-related neovascular macular degeneration, *ROI* return on investment, *NA* not applicable

for fellow eyes receiving Zx supplementation. This occurred because caregiver societal costs and medical cost differences between the cohorts receiving and not receiving Zx did not differ appreciably when fellow-eye nAMD conversion incidence rate differences decreased to 5% or less.

Five-Year Model, Direct Ophthalmic Medical Cost Perspective

Changing the model time from 11 to 5 years produced a mean 0.10 QALY gain from Zx supplementation decreasing second-eye conversions in baseline unilateral nAMD cases. The direct ophthalmic medical costs, including Zx costs, expended during this time were $5081 for the cohort receiving Zx supplementation and $6167 for the cohort not receiving Zx supplementation, resulting in a comparative direct ophthalmic medical cost of −$1086 for Zx supplementation. The direct ophthalmic cost perspective CUR was (−$1086/0.10 =) −$10,860 QALY. Zeaxanthin supplementation was dominant vs. none, since Zx supplementation yielded greater patient value for less cost.

Five-Year Model, Societal Cost Perspective

The 0.10 QALY gain remained unchanged. The societal costs associated with Zx supplementation were (1) −$778 in direct non-ophthalmic medical costs, (2) $0 in caregiver costs, and (3) −$896 in wage loss, for a total of −$1674. In conjunction with the direct ophthalmic medical cost of −$1086, the total societal cost for Zx supplementation was (−$1674 + $1086 =) −$2760 per participant with baseline unilateral nAMD. The 5-year model societal CUR was thus (−$2760/0.42 =) −$6571/QALY, and Zx supplementation was again dominant versus no supplementation. No extra direct medical costs were accrued since we demonstrated that no time of life was saved.

Eleven-Year Model, Direct Ophthalmic Medical Cost Perspective Utilizing Bevacizumab Injections Instead of Triple Therapy

When intravitreal injections of bevacizumab were substituted for triple therapy at a frequency commonly utilized in the US for nAMD [1], and assuming visual outcomes were the same with only bevacizumab injections and triple therapy herein, the total direct ophthalmic medical cost per patient for second-eye therapy in the mean patient not receiving Zx supplementation averaged $7315, whereas the average per-patient second-eye cost for those receiving Zx supplementation was $4126. Adding the $3431 Zx cost to this cost ($4126) resulted in an average $7557 cost. Subtracting the cost for no Zx supplementation from the cost for Zx supplementation resulted in a ($7557–$7315 =) $242 direct ophthalmic medical cost when Zx supplementation was undertaken. This resulted in a direct ophthalmic cost-utility ratio of ($242/0.42 QALY =) $576/QALY, slightly higher than the −$576/QALY observed in our 227 patient, baseline unilateral nAMD cohort.

Cost–Benefit Analysis

It is estimated that 168,400 US cases of nAMD occurred in 2018 [52]. Extrapolating this number using the 327.1 million population in 2018 to 331.0 million in 2020 [51] suggests that 170,400 new nAMD cases developed in 2020.

If 67% of new patients presented with unilateral first-eye nAMD involvement, as was the case herein, the new 2020 US unilateral, first-eye nAMD patient number is (170,400 × 0.67 =) 114,173.

The cost–benefit ratio was calculated herein by dividing the $52,530 societal cost gain (benefit) per patient with Zx supplementation by the $3431 cost of Zx supplementation. The result was ($52,530/$3431 =) a discounted, 1531% 11-year return on investment (ROI).

The 11-year societal gain from treating all 114,173 patients with baseline unilateral nAMD was (114,173 × $52,530 =) $6.0 billion, while the Zx supplementation cost for the same cohort was (114,173 × $3431 =) $391.7 million. Thus, ($6.0 billion/$391.7 million) also yielded a 1531% ROI. This was equivalent to a 1-year ROI of 31.3%. When the difference between the relative conversion rate difference of fellow eyes between the Zx-treated and non-Zx-treated cohorts decreased to approximately 5%,

caregiver cost differences became negligible. Minimal, if any, money was returned from Zx supplementation, as shown in the societal cost perspective cost–benefit sensitivity analysis in Table 8.

Average Cost-Utility Analysis of the Entire 337 Baseline Cohort Including Unilateral and Bilateral nAMD Cases

All treated 337 baseline eyes (Table S5) had mean $20/125^{+1}$ baseline vision and mean $20/160^{+1}$ vision at 5 years, carried forward to 6–11 years since data have shown that many VEGF-I-treated nAMD eyes maintain stable baseline vision over 10 years [53] (Table 9). For the historical comparative control cohort receiving no treatment whatsoever, mean nAMD vision was taken from 2-year clinical trial data [1], then by modeling from years 3–11 according to the Lineweaver-Burk meta-analysis by Shah and DelPriore [41] (Table 9).

The weighted average of QALY gain per patient obtained with the direct ophthalmic cost perspective contribution in the entire 337-patient cohort for the average patient presenting with unilateral nAMD (first-eye model) who gained value because there was less second-eye conversion to nAMD from Zx was (67% × 0.42 QALY =) 0.281 QALY. The QALY contribution per patient (33% of the entire 337 cohort) with baseline second-eye or bilateral involvement (second-eye model) was (33% × 1.095 QALY =) 0.361 QALY. Adding the baseline first-eye model contribution per patient QALY gain to that of the presenting second-eye model patient QALY gain indicated that the mean 337-participant cohort patient gained (0.281 QALY + 0.361 QALY =) 0.643 QALY (12.4% QALY gain over no therapy). The 1.045 QALY gain, a 21.1% gain, for participants presenting with baseline second-eye involvement was calculated by comparing the mean utility based upon the mean vision of Zx-treated participants and non-treated patients at each year of the 11-year model (Table 10) and adjusting for one year of life lost from decreased vision associated with no treatment for nAMD.

The direct ophthalmic medical cost perspective, average (compared to no therapy) CUR for triple therapy costs in 337 nAMD patients in addition to Zx supplementation costs in eyes that presented with baseline unilateral nAMD was ($14,213)/0.643 QALY =) $22,105/QALY (Table 10).

The 337-patient societal cost perspective average cost-utility ratio integrated both societal costs and the extra direct medical costs incurred by a 0.25 mean added year of life in the first-eye model and 1.0 year of life gain [1] in the second-eye model (Table 10). The mean societal cost accrued for each study entrant, integrating the direct ophthalmic medical costs and the extra medical costs from prolonged life was −$68,588, the same amount returned to society over 11 years. The societal average cost-utility ratio was therefore (−$68,588/0.643 =) −$106,669/QALY, indicating that therapy was dominant vs. no therapy.

Cost–Benefit of Triple Therapy with Zx Supplementation

At a net societal treatment cost of −$68,293 per patient, the annual saving versus no nAMD therapy from treating the 2020 annual cohort of 170,400 nAMD patients with triple therapy and oral administration of Zx in baseline unilateral nAMD cases theoretically was (−$68,293 × 170,400 =) $11.78 billion returned to society over 11 years. This resulted in a ($68,293/$14,214 =) 480% 11-year ROI for the 11-year direct ophthalmic medical costs, including Zx supplementation. We did not model the entire 337-patient cohort gain of $68,293 utilizing the direct cost of Zx supplementation alone since we could not be certain that Zx benefitted baseline participants with fellow-eye nAMD.

DISCUSSION

It was demonstrated in a 2-year randomized clinical trial that 20 mg daily of oral Zx supplementation significantly decreases conversion of atrophic AMD fellow eyes to nAMD in patients presenting with unilateral nAMD. The results herein further support those data [4, 5]

and a very favorable cost-utility ratio for Zx supplementation in unilateral nAMD cases. We did not factor vision into the analysis since we noted similar vision outcomes after nAMD intravitreal treatment with and without Zx supplementation [6]. Because our baseline mean vision differed from that in monotherapy clinical trials [1], and because earlier treatment yields a better vision outcome [42], we also did not have ideal 5-year comparators for vision.

Zeaxanthin Incremental CUA

In a comparative interventional triple therapy study, we previously demonstrated that Zx decreased the 2-year fellow-eye nAMD conversion rate ($p = 0.03$) [5]. A 2-year randomized clinical trial comparing Zx supplementation and none showed that the Zx–decreased conversion rate relationship was stronger yet ($p = 0.02$) [6]. Widomska and colleagues [54] noted greater singlet oxygen quenching by Zx than lutein, suggesting a mechanism which might decrease nAMD occurrence.

Cost-Effectiveness

An oft-quoted US cost-effectiveness upper limit for healthcare interventions is \$100,000/QALY, though the US has no formal standards [17]. The World Health Organization upper limit is 3 × gross domestic product (GDP) per capita (US 2020 = \$195,073), while < 1 × GDP per capita (US 2020 = \$65,024) is considered very cost-effective [17]. Zx supplementation with unilateral nAMD is incrementally cost-effective versus no Zx supplementation, and baseline triple therapy with Zx supplementation versus no nAMD therapy for all comers is also cost-effective. The contribution of Zx supplementation for patients presenting with baseline second-eye nAMD involvement, however, is uncertain.

Average prior CURs for nAMD anti-VEGF monotherapy [1] for all presenting new nAMD eyes were noted to be: bevacizumab = \$11,033/QALY, ranibizumab = \$79,600/QALY and aflibercept = \$44,801/QALY, versus our \$22,105/QALY with triple therapy/Zx, though 76 of our 399 (19%) participants had baseline 20/400–20/800 vision, versus baseline vision ≥ 20/320 in monotherapy trials [1]. Our \$22,105/QALY CUR for triple therapy/Zx for all nAMD entrants is closer to monotherapy with bevacizumab based on CATT [1, 2] than to aflibercept or ranibizumab.

Zeaxanthin and Conversion Incidence

Our 5-year study demonstrated a decreased incidence of conversion to nAMD in second eyes of 22% versus a 48% conversion incidence ($p < 0.0001$) in CATT [29]. The 5-year, 42%, MPS conversion incidence [30] also differed dramatically from our 22% incidence ($p < 0.0001$). The Three Continent AMD Consortium Report [47] noted a 44% 5-year fellow-eye conversion rate ($p < 0.0001$) for someone presenting with unilateral nAMD. We believe these studies without Zx treatment support the concept that Zx supplementation decreases nAMD conversion.

Vision

While some studies suggest that carotenoid supplementation has improved vision [55], we could not demonstrate this in our previous clinical trial [6] or herein except by the mechanism of Zx supplementation reducing the incidence of nAMD in fellow eyes [6]. We are therefore uncertain whether Zx supplementation for eyes that already have nAMD leads to improved vision above that obtained with intravitreal injection therapy without Zx-supplementation.

Intravitreal Injections

While anti-VEGF monotherapy prevents PDT adverse events, ranibizumab and bevacizumab 11-year per-eye nAMD therapies both required a mean of 51.2 intravitreal injections [1], versus our triple therapy's 19.3 intravitreal injections for bevacizumab and dexamethasone combined, approximately 38% of the intravitreal injections needed with anti-VEGF monotherapies [1].

Bilateral nAMD Treatment

We believe bilateral treatment, when indicated in the first-eye model, gives superior binocular vision, maximizes quality of life, and decreases overall blindness. Half of our baseline unilateral eyes receiving triple therapy had 5-year vision $\leq$ 20/200. Treating patients bilaterally, however, yields $\leq$ 20/200 vision in 25% (50% $\times$ 50%) of patients, rather than 50% [5]. Thus, we believe bilateral nAMD therapy should be undertaken when indicated.

Mechanisms of Zx Action [54]

Macula-concentrated Zx comprises 75% of retinal carotenoids, versus the peripheral 25% lutein component. Unlike lutein, Zx reduces light-induced cone/rod apoptosis in quail. Zeaxanthin also filters energy-containing blue light to a greater extent than lutein. This phenomenon limits destructive singlet oxygen production thought to play a role in nAMD formation. Furthermore, Zx may also promote macular retinal pigment concentration and increased cell survival [55].

Adverse events We observed no adverse events with Zx and are unaware of any reported. Rodents given 1000 mg/kg/day and dogs on 400 mg/kg/day also had none. The European Nutrition, Novel Foods and Food Allergens Panel recommended a safety factor not to exceed 53 mg/day for a 70-kg adult, well above our 20 mg daily dose [56].

Prevention Trumps Treatment

Our incremental CUA demonstrates that nAMD second-eye prevention is superior to treatment in baseline unilateral nAMD cases [1]. Not only does Zx supplementation prevention yield a greater QALY gain versus no supplementation, but it is less costly and results in a large ROI for the Zx supplementation cost. It has been previously shown that 80% of cost saving is returned to patients [1]. From a societal cost perspective, $63,135 is saved in caregiver costs, and most of $52,530 is returned to baseline unilateral nAMD patients, who spend less due to better vision from decreased nAMD conversion.

Nonetheless, because Zx supplementation saves 0.25 life-years at age 90 by reducing fellow-eye nAMD, there is $10,847 excess non-ophthalmic, direct medical cost over the 0.25 years accrued to insurers. This illustrates the important issue that time of life saved can increase overall medical costs [1]. For example, if all smokers stopped smoking, healthcare costs accrued with age would exceed those saved from not smoking by 15 years after tobacco cessation [57].

Prevention is superior to treatment for other conditions as well, including heart transplant rejection [58], recurrent ischemic stroke [59], wound site infection [60], malaria [61] and others.

Study Limitations

Comparing 11-year, unilateral nAMD treatment cohort data in patients with and without Zx supplementation would be ideal, rather than using post hoc historical control data with 2 mg Zx supplementation daily [6, 62]. We believe, however, that new drugs, delivery systems and other advances make the likelihood of an 11-year clinical trial low. Furthermore, deleting a daily 2-mg Zx dose now from unilateral nAMD cases is unethical [6, 62, 63]. That said, our previous 2-year clinical trial [5] did demonstrate a risk reduction for nAMD occurrence with 20-mg Zx supplementation versus a cohort control not receiving Zx supplementation when both took daily AREDS2 supplements containing 2 mg of Zx.

Testing each of the different anti-VEGF nAMD monotherapies with and without Zx-supplementation might also be highly desirable. The DENALI [64] and MONT BLANC [65] studies, however, both demonstrated similar vision outcomes with ranibizumab versus ranibizumab with PDT. From this information, our earlier clinical trial results [5, 6], and the current analysis, we believe the evidence is sufficiently robust to suggest a beneficial effect of Zx independent of monotherapy or triple therapy. We are not aware that PDT, intravitreal

corticosteroids, or anti-VEGF monotherapies given unilaterally inhibit fellow-eye nAMD.

The fact that bevacizumab was the only anti-VEGF monotherapy we utilized could be a drawback, though vision outcomes for the three most commonly used intravitreal anti-VEGF monotherapies (ranibizumab, aflibercept and bevacizumab) have been shown to be similar [1]. CATT also previously showed that the risk of developing nAMD in fellow eyes is independent of whether ranibizumab or bevacizumab is used in initial eyes [2, 29, 30].

We are uncertain whether the use of predominantly AREDS2 supplements in our participants, which added 2-mg oral zeaxanthin daily to the 20-mg Zx supplemental therapy dose is relevant. The CATT participants (enrolled during 2008–2009) used supplements in 90% of cases but did not have the AREDS2 formula with 2 mg zeaxanthin/10 mg lutein available until 2013. The AREDS2 Research Group Report No. 3 [6] noted that the zeaxanthin 2 mg/lutein 10 mg combination did not influence vision, though the 10-year hazard ratio for progression to late AMD comparing lutein/zeaxanthin to no lutein/zeaxanthin was 0.91 ($p = 0.02$). Our 5-year hazard ratio was approximately 0.46 ($p < 0.0001$) with 20 mg of additional daily Zx supplementation over the 2 mg in AREDS2 supplements.

Study Strengths

A strength of this study is the 89% 5-year follow-up on the 227-patient unilateral nAMD cohort and 90.5% follow-up on all 337 baseline patients, both high relative to other studies [29, 30].

Our patient-acquired ocular utilities are also a strength. Reliable and validated, they are typically unaffected by age [16, 22, 23], gender [16, 22], educational level [16, 22], underlying ocular disease [24], systemic comorbidities [25, 26], or race [66], and are similar in multiple countries [66].

It bears repeating that our 2-year, triple-blind, randomized clinical trial demonstrated that Zx supplementation in unilateral baseline nAMD cases significantly reduced nAMD conversion in fellow eyes ($p = 0.02$) [6]. The current study was conducted to ascertain whether the nAMD reduction rate persisted at 5 years. While we lacked an internal 5-year control cohort, we believe that our data compared to CATT [2, 28, 39] and other clinical trial [31, 45, 47] results strongly support the protective effect of Zx in preventing nAMD.

CONCLUSIONS

Participants with baseline unilateral nAMD on long-term oral Zx supplementation demonstrated a reduction in fellow-eye nAMD conversion versus historical controls not receiving Zx supplementation at 5 years. Supplementation with zeaxanthin to prevent fellow-eye nAMD is extremely cost-effective by conventional US standards, returns monies to society, and likely prevents loss of life-years from poorer vision. Zx supplementation in an 11-year cohort of US unilateral nAMD patients would return a net $6.0 billion to society, predominantly to patients.

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Compliance with Ethics Guidelines. The Wills Eye Hospital IRB approved utility acquisition, and adherence to the Declaration of Helsinki and its amendments was observed. The SSM Health Care Institutional Review Board approved triple therapy with Zx-supplementation (approval number 14–07-0540). The ClinicalTrials.gov identifier for the original randomized clinical trial was NCT 01527435.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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