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ORIGINAL RESEARCH

Patient Preferences Associated with Anti-Vascular Endothelial Growth Factor Therapies for Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema

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Purpose: To evaluate treatment-related preferences among patients receiving intravitreal anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (nAMD) or diabetic macular edema (DME).

Patients and Methods: We conducted a prospective survey of patients with nAMD or DME treated at one of three US-based retina clinics. Prior to survey development, small focus groups with anti-VEGF-treated patients identified five treatment-related "attributes" considered important to those with nAMD or DME: vision outcomes, cost to the insurance provider, cost to the patient, frequency of treatment, and drug label status. Attributes were described using two to three "levels", and hypothetical treatment profiles were generated by assigning one level to each attribute. Surveyed patients were asked to indicate their preference between two given treatment profiles for a total of eight pairwise comparisons. Discrete choice conjoint analysis was performed to estimate the relative importance of each attribute for the overall patient cohort, and for subgroups stratified by age and highest education level.

Results: Among 300 respondents, 54% were female, 78% were aged ≥65 years, and 67% indicated that high school was their highest level of education. Achieving good vision was the most important factor associated with anti-VEGF therapy for nAMD or DME (relative importance, 40.4%), followed by low cost to the patient, on-label drug status, less frequent treatment intervals, and low cost to the insurance provider (23.1%, 21.3%, 12.2%, and 3.0%, respectively). When patients were stratified by age group or highest education level, preference trends across subgroups were generally comparable with the overall cohort.

Conclusion: Our data suggest that treatment decisions regarding anti-VEGF therapies for nAMD or DME are most likely driven by their efficacy, and that patients may be willing to accept less desirable treatment attributes, such as increased cost and/or injection frequency, in order to achieve superior vision outcomes.

Keywords: anti-VEGF therapy, conjoint analysis, diabetic macular edema, neovascular age-related macular degeneration, patient preferences

Introduction

Diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) are leading causes of blindness among working-age and elderly populations, respectively. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is considered the standard of care for nAMD and DME,[1,2] with four agents

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commonly used in current clinical practice: US Food and Drug Administration (FDA)–approved ranibizumab and aflibercept for nAMD and DME; FDA-approved brolucizumab for nAMD; and off-label bevacizumab for both conditions.[3–6] Landmark trials suggest that these agents have comparable safety and efficacy in their respective indications;[7–12] therefore, treatment preferences among physicians and patients may instead be driven by other factors, such as differences in cost and labeled injection frequency. For example, monthly injections of ranibizumab 0.5 mg and 0.3 mg are FDA-approved for the treatment of nAMD and DME, respectively,[3] whereas aflibercept 2.0 mg is indicated every 8 weeks after three to five monthly loading doses,[4] and brolucizumab 6.0 mg is recommended every 8–12 weeks after three monthly loading doses in patients with nAMD.[5] Moreover, wholesale acquisition costs for these on-label therapies currently range between $1170–$1950 per dose, while the cost of repackaged bevacizumab 1.25 mg has been estimated at $50–$60.[13–16]

As treatment decisions become more complex and the delivery of patient-centered care becomes increasingly important, physicians are often encouraged to involve patients in decisions regarding their health. This paradigm shift towards shared decision-making has been driven by evidence that treatment adherence, patient satisfaction, and clinical outcomes are improved when patient preferences are taken into consideration.[17–19] Patient preferences in health care are often evaluated using conjoint analysis, a survey-based technique used to quantify the value placed on characteristics (or "attributes") related to a health product or service. Through a series of trade-off exercises, patient preferences are used to generate utility values that demonstrate the relative importance of each attribute in treatment decisions.[20,21] Conjoint analyses have been used to elicit patient preferences for the management of several ophthalmic conditions, including glaucoma,[22,23] cataracts,[24] diabetic retinopathy,[25] and nAMD.[26]

In light of the similarities and differences between anti-VEGF therapies for nAMD and DME, we sought to better understand the treatment-related attributes that patients consider most important in current clinical practice. This prospective survey and conjoint analysis aimed to elicit and evaluate patient preferences among those receiving intravitreal anti-VEGF therapy for the management of nAMD or DME.

Materials and Methods

Study Design and Patient Population

This was a prospective study of patients with nAMD or DME surveyed at one of three University Retina clinics (Bedford Park, IL; Lemont, IL; Oak Forest, IL) between August and December 2018. Patients aged ≥18 years and receiving intravitreal anti-VEGF therapy for nAMD or DME were eligible to participate; non-English-speaking patients and those with an impaired ability to understand and provide verbal consent were excluded. Details of the study were explained to those deemed eligible by the investigators, and patients who provided verbal consent completed the electronic survey during their scheduled clinic visit. Patients completed the survey anonymously and no identifiable data were collected; therefore, this study was exempted from requiring ethical approval by the Quorum Review institutional review board.

Survey Design

Prior to survey development, small focus groups with patients who had received three or more anti-VEGF injections (three groups of five patients) were conducted to identify treatment-related attributes that may be considered important to those with nAMD or DME. Five attributes were identified and subsequently evaluated in the survey: vision outcomes with treatment, cost of treatment to the insurance provider, cost of treatment to the patient, frequency of treatment, and drug label status.

The survey was developed and administered using SurveyAnalytics software (QuestionPro Inc, Austin, TX).[27] The five treatment attributes to be assessed were each assigned two to three "levels" to reflect differing features of anti-VEGF therapy; attributes, levels, and definitions provided to patients are described in Table 1. During the survey, patients were asked to indicate their preference between two hypothetical anti-VEGF treatment profiles, each comprising a set of attributes described by a set of levels (Figure 1). Based on the number of treatment attributes and levels assessed in this study, 48 hypothetical treatment profiles are available for comparison; however, it is not feasible for patients to meaningfully consider every possible combination in one survey. As such, patients completed eight pairwise comparisons in this study, which were dynamically assigned by the software using a D-optimal design algorithm.

Table 1 Anti-Vascular Endothelial Growth Factor Treatment Attributes, Levels, and Definitions Provided to Patients

Attribute/Level	Definition
Vision	
Good	Able to read small print in magazines/newspapers with good lighting.
Moderate	Able to recognize faces and read newspaper headlines/writing on TV (medium print).
Poor	Able to navigate around a room and make out large objects, but not able to see faces/TV/read clearly.
Cost per treatment to the insurance company	
Low cost	$50
High cost	$1200
Cost per treatment to you, the patient	
Low cost	$5
High cost	$70
Frequency of treatments: How often you will have to come to the clinic to be assessed for possible treatment.	
More frequent	Every 4 weeks
Less frequent	Every 8 weeks
Drug label status: A drug can be used to treat different medical problems. If the US Food and Drug Administration (FDA) has approved the medication to be used for a certain medical problem, this is called "on-label." Many drugs are widely used "off-label." For example, aspirin is commonly used "off-label" to prevent heart attacks and strokes.	
On-label	Medication is approved by the FDA to treat this disease.
Off-label	Medication has not been approved by the FDA to treat this disease.

Statistical Analysis

Demographic data collected in the survey (age, sex, and highest level of education) are presented using descriptive statistics. Discrete choice conjoint analysis was performed with SurveyAnalytics software, which used survey responses to generate utility values for each attribute level using multinomial logistic regression and Nelder–Mead simplex methodology.[28] The relative importance of each attribute was expressed as a percentage by dividing the utility range for a given attribute (ie, highest minus lowest utility level) by the sum of utility ranges for all attributes and multiplying by 100. The relative importance of the five attributes was calculated for the overall patient cohort, and for subgroups stratified by age and highest education level.

Results

Study Population

In total, 300 patients receiving intravitreal anti-VEGF therapy for nAMD or DME completed the survey. Patient demographics at the time of the survey are summarized in Table 2. Fifty-four percent of patients were

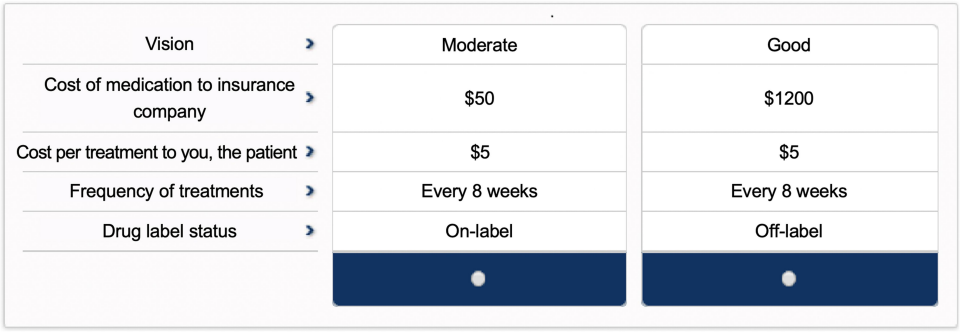

Figure 1 Illustrative treatment profile comparison presented to patients.

Table 2 Baseline Patient Demographics

Baseline Variable	Surveyed Cohort N=300
Female, n (%)	162 (54.0)
Age, n (%)	
18–39 years	4 (1.3)
40–64 years	62 (20.7)
65–79 years	132 (44.0)
≥80 years	102 (34.0)
Highest level of education, n (%)	
Did not complete high school	25 (8.3)
High school	201 (67.0)
Undergraduate degree	57 (19.0)
Graduate/professional degree	14 (4.7)
Chose not to answer	3 (1.0)

female, the majority (78%) were aged ≥65 years, and high school was the highest level of education achieved for 67% of the cohort.

Overall Preferences

Conjoint analysis found that achieving good vision was the most important attribute for patients receiving intravitreal anti-VEGF therapy for nAMD or DME (Table 3). The relative importance of good vision was 40.4% for the overall cohort, followed by cost to the patient (preference for low cost; 23.1% relative importance), and drug label status (preference for on-label status; 21.3% relative importance). The least important attributes were treatment frequency (preference for less frequent treatment; 12.2% relative importance) and cost to the insurance provider (preference for low cost; 3.0% relative importance).

Preferences by Age

When patients were stratified by age, good vision remained the most desirable feature of intravitreal anti-VEGF therapy across age groups (Figure 2). Compared with other age groups, patients aged 18–39 years placed greater importance on vision (63% vs 39–43% relative importance) and placed less importance on treatment frequency (0% vs 9–16% relative importance); however, these results are based on a small sample size (n=4) and should be interpreted with caution. The relative importance of drug label status was greater for those aged

Table 3 Utility Values and Relative Importance of Anti-Vascular Endothelial Growth Factor Treatment Attributes

Treatment Attribute	Level	Mean Utility Value	Relative Importance
Vision	Good Moderate Poor	0.95 0.02 −0.97	40.4%
Cost to patient	Low cost High cost	0.55 −0.55	23.1%
Drug label status	On-label Off-label	0.50 −0.50	21.3%
Treatment frequency	More frequent Less frequent	−0.29 0.29	12.2%
Cost to insurance provider	Low cost High cost	0.07 −0.07	3.0%

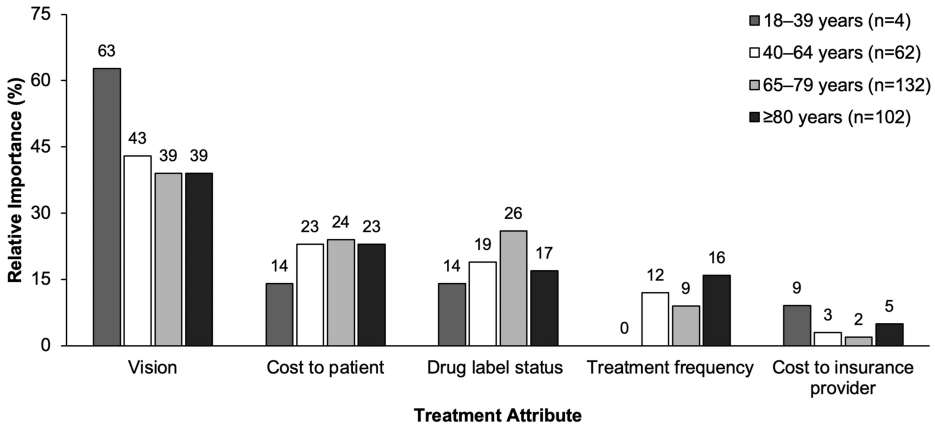

Figure 2 Relative importance of treatment attributes for patients receiving intravitreal anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration or diabetic macular edema, stratified by age.

65–79 years than other age groups (26% vs 14–19% relative importance); otherwise, preference trends across age groups were generally consistent with the overall cohort.

Preferences by Education Level

The relative importance of treatment attributes for patients stratified by highest education level is presented in Figure 3. Vision remained the most important factor for patients who had completed high school or an undergraduate degree (39% and 50% relative importance, respectively). The importance of cost to the patient was comparable to vision outcomes among those who did not complete high school (33% vs 32% relative importance), while patients with a graduate/professional degree placed slightly greater importance on drug label status than vision outcomes (31% vs 27% relative importance). Patients who completed a graduate/professional degree also considered treatment frequency to be more important than any other subgroup (21% vs 1–13% relative importance), while those who did not complete high school placed greater importance on cost to the insurance provider than treatment frequency (12% vs 3% relative importance).

Discussion

Our conjoint analysis of 300 patients in current clinical practice revealed that vision was the most important factor when considering intravitreal anti-VEGF therapies for nAMD or DME. These data suggest that treatment decisions regarding anti-VEGF agents are most likely driven by their efficacy, and that patients may be willing to accept

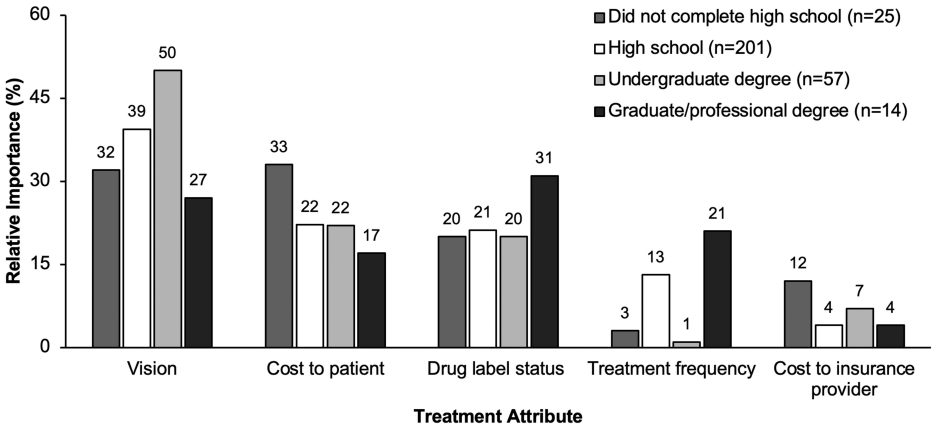

Figure 3 Relative importance of treatment attributes for patients receiving intravitreal anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration or diabetic macular edema, stratified by highest education level.

less desirable treatment attributes, such increased cost and/or injection frequency, in order to achieve superior vision outcomes.

Our results coincide with previous analyses that have demonstrated the importance of vision outcomes among patients receiving treatment for nAMD or DME.[26,29,30] In particular, Baxter et al used conjoint analysis to evaluate preferences regarding nAMD management in UK clinical practice and found that patients ranked good vision above a one-stop clinic setup (whereby injections are administered during the same scheduled visit), less frequent visits, clinic waiting time, drug label status, cost to the National Health Service, and the qualification of the injector (doctor vs nurse practitioner).[26] Similarly, a discrete choice experiment by Mueller et al found that "change of visual acuity" was the most important factor among patients receiving anti-VEGF therapy for nAMD in Germany, followed by "waiting, treatment, and travel time", and "treatment scheme" (comparing injections every 4 weeks, every 8 weeks, and as-needed with monthly visits).[29] Due to the manner in which health care is funded in the UK and Germany, costs incurred to patients were not considered in these studies; however, the results of our analysis suggest that when out-of-pocket costs are factored into treatment decisions, patients are nevertheless willing to trade-off increased costs for improved vision gains. Our findings are also consistent with other conjoint analyses that identified vision-related outcomes as the most important factors among patients with glaucoma,[22] cataracts,[24] and diabetic retinopathy;[25] collectively demonstrating the high value that patients with ophthalmic conditions place on preserving vision to maintain their quality of life.

Cost of treatment to the patient and drug label status were the second- and third-most important attributes in our analysis, respectively. Assuming that vision outcomes are generally similar between off-label bevacizumab and its on-label comparators for nAMD or DME,[7–10] our findings suggest that the significantly lower cost of off-label bevacizumab may favor its use in clinical practice. However, the influence of treatment costs on patient preferences may be substantially reduced when costs are covered by insurance providers, which was found to be the least important factor in our analysis. For patients with DME, willingness to accept an off-label treatment might also be dependent on visual acuity, based on evidence that off-label bevacizumab may be less efficacious than on-label anti-VEGF therapies in those with lower baseline vision.[7,8]

Treatment frequency was found to be the fourth-most important factor in our conjoint analysis, suggesting that many patients are prepared to tolerate an intensive treatment regimen in exchange for good vision. Previous studies have similarly demonstrated the high treatment burden that patients will accept to preserve their vision, including Mueller et al who estimated that patients with nAMD were willing to spend an additional 12.7 hours per clinic visit to achieve stable rather than worsening vision, and 21.2 hours to improve their vision outcomes.[29] In a survey that compared patient preferences associated with focal grid laser and intravitreal anti-VEGF therapy for DME, Mason et al found that 83% of patients were prepared to receive 15–16 injections in order to gain two lines of Snellen visual acuity, 86% would sacrifice zero lines of vision to receive 4 lasers versus 15–16 injections, and 76% would be willing to receive treatment 12 times per year to maintain their vision.[30] Given that endophthalmitis is a potentially vision-threatening complication of intravitreal injection therapy,[31] further studies are needed to examine whether an increasing risk of endophthalmitis may impact a patient's willingness to accept frequent injections for improved vision outcomes.

We stratified patients by age to examine whether advancing age, and possibly Medicare eligibility, may influence anti-VEGF treatment preferences; however, the relative importance of each attribute was similar between age subgroups. Moreover, preference trends for patients grouped according to highest education level were generally comparable with that of the overall cohort. These findings indicate that decisions regarding anti-VEGF therapy for nAMD and DME are driven by similar factors across all patients, irrespective of demographic profile.[25] One notable exception was the subgroup of patients with graduate/professional degrees, who ranked drug label status as the most important attribute of anti-VEGF therapy for nAMD and DME and placed greater relative importance on treatment frequency than any other education level subgroup. These observations are based on a small sample size (4.7% of the overall cohort) and require validation in larger studies; nevertheless, they may suggest that patients with higher degrees have a greater awareness of the research and regulatory processes that ensure the safety and effectiveness of approved medications. Moreover, these patients may be less able to attend frequent treatment visits due to employment or other lifestyle reasons and are thus more willing to absorb increased costs in exchange for fewer injections.

Treatment preferences reported herein are based on a small, English-speaking patient population surveyed across three US-based retina clinics; therefore, further studies are needed to validate our survey and assess the generalizability of our results in other patient groups, countries, and/or health care systems. Patient demographics collected in this study were limited to age, sex, and education level; as such, we were unable to compare preferences between nAMD and DME cohorts, nor examine the influence of other patient-related factors on anti-VEGF treatment decisions (eg, visual acuity, ethnicity, treatment experience, and insurance type). As conjoint analyses are inherently limited by the number of attributes that patients can meaningfully rank in one survey, further studies are needed to assess the importance of other treatment-related factors, such as the safety profiles and adverse events associated with different anti-VEGF therapies. Finally, although patients preferred vision to treatment frequency when monthly and bimonthly regimens were compared, our survey was conducted prior to the FDA approval of brolucizumab for nAMD (indicated every 8–12 weeks[5]) and did not consider other extended dosing schedules, including as-needed and treat-and-extend protocols. Given that these regimens were developed to individualize therapy and/or reduce treatment burden in clinical practice,[32] future studies may seek to determine their impact on anti-VEGF treatment choices; however, our findings suggest that a patient's preference for fewer injections will be largely dependent on the vision outcomes achievable with these strategies.

In conclusion, patients with nAMD or DME placed greater importance on vision outcomes than treatment costs, drug label status, and injection frequency when receiving intravitreal anti-VEGF therapy for the management of these conditions. These preferences may be used to guide treatment decisions between patients and physicians, promote patient-centered care in ophthalmology, and ultimately improve health outcomes among patients with nAMD or DME.

Abbreviations

DME, diabetic macular edema; FDA, US Food and Drug Administration; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

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Disclosure

Dr Meena George has served on the advisory board of Allergan, outside the submitted work. Dr Veeral S Sheth has served as a consultant for Alimera, Eyepoint, Genentech, Inc., Notal Vision, and Novartis; and reports personal fees from Genentech, Novartis, Alimera, Notal Vision, and Eyepoint, and grant support from Apellis Pharmaceuticals, Chengdu Kanghong Biotechnology Co., Ltd., Graybug Vision, Inc., Ionis Pharmaceuticals, Outlook Therapeutics, and Regeneron, outside the submitted work. The authors report no other conflicts of interest with respect to this work.

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