RETINA SPECIALISTS TREATING
AGE-RELATED MACULAR
DEGENERATION RECOMMEND DIFFERENT
APPROACHES FOR PATIENTS THAN THEY
WOULD CHOOSE FOR THEMSELVES

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Purpose: To evaluate the presence of cognitive biases among retina physicians when recommending treatment options for exudative age-related macular degeneration.

Methods: Two random samples of retina specialists were surveyed regarding their treatment and dosing regimen choices among three anti-vascular endothelial growth factor biologics (afibercept, bevacizumab, and ranibizumab). One group was asked to provide recommendations for a standardized hypothetical patient with exudative age-related macular degeneration, whereas the other group was asked to provide recommendations as if they themselves were the standardized hypothetical patient with exudative age-related macular degeneration.

Results: Two hundred and twenty-six respondents (28.3%) completed the survey and were divided equally between the survey groups. For patients, most physicians recommended bevacizumab (52.2%), but when choosing for themselves, physicians were divided equally among all 3 biologics ($P=0.011$). The results were influenced by geographical location of the physician but not by the gender or length of practice. Furthermore, physicians differed in dosing regimen selection with the majority (73%) choosing treat and extend for patients, whereas only 63% selected this regimen for themselves ($P=0.004$).

Conclusion: When considering cases of exudative age-related macular degeneration, physicians would recommend different treatments for themselves than they would for a patient.

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Current treatment for choroidal neovascularization secondary to exudative age-related macular degeneration (AMD) directly targets the pathologic mediators of AMD. Anti-vascular endothelial growth factor (anti-VEGF) agents have become the standard of care.

Three anti-VEGF biologics for AMD treatment (afibercept, bevacizumab, and ranibizumab) are commonly used, and prospective clinical trial data support utilization of any of the three anti-VEGF treatments. Given the similar nature of the commercially available anti-VEGF agents, it is not surprising that a range of practice patterns exists.

Various studies have shown that physician treatment recommendations factor heavily into patient decisions, but these recommendations can often be subject to cognitive biases. In this study, we tested whether recommendations made by retina specialists regarding treatment for AMD were subject to such biases. We conducted two randomized experiments asking physicians to choose which treatment they would recommend for either a hypothetical patient with AMD or
for themselves. Based on previous studies in other medical specialties, we hypothesized that there would be discrepancies in the treatment physicians would choose for themselves compared with their patients. Furthermore, we also hypothesized that the manner in which physicians use these compounds would vary based on whether they were treating themselves or a patient.

Methods

We surveyed two random samples of retina specialists selected from the American Society of Retina Specialists membership database, the most complete listing of retina specialists in the United States. The survey groups were evenly balanced by location to account for potential regional differences in prescribing habits. We provided each group with a clinical scenario and collected subsequent responses through an electronic survey managed by Survey Monkey software. One group was asked to provide treatment and dosing regimen recommendations among three anti-VEGF agents for a standardized hypothetical patient with exudative AMD, whereas the other group was asked to provide treatment and dosing regimen recommendations as if they themselves were the standardized hypothetical patient with exudative AMD. The participants were not aware that a similar survey would be asked to a matched group of their colleagues to reduce bias in their responses. The survey questions were presented in the following manner:

**Scenario 1**

A 70-year-old presents with 20/100 visual acuity in the left eye secondary to exudative AMD. There is minimally classic choroidal neovascularization seen on angiography, and subretinal fluid and cystoid macular edema on optical coherence tomography. The right eye demonstrates high-risk drusen. The patient has no significant medical history. Which anti-VEGF agent would you treat this patient with?

1. Afibercept (Eylea)
2. Bevacizumab (Avastin)
3. Ranibizumab (Lucentis).

How would you treat this patient?

1. Monthly injections for at least 1 year
2. Loading injections followed by as needed (PRN) treatment
3. Loading injections followed by “treat and extend.”

**Scenario 2**

Imagine that you are the following patient. You are a 70-year-old who develops 20/100 visual acuity in the left eye secondary to exudative AMD. There is minimally classic choroidal neovascularization seen on angiography, and subretinal fluid and cystoid macular edema on optical coherence tomography. Your right eye demonstrates high-risk drusen. You have no significant medical history. Which anti-VEGF agent would you treat yourself with?

1. Afibercept (Eylea)
2. Bevacizumab (Avastin)
3. Ranibizumab (Lucentis).

How would you treat yourself?

1. Monthly injections for at least 1 year
2. Loading injections followed by as needed (PRN) treatment
3. Loading injections followed by “treat and extend.”

**Covariates and Data Analysis**

All data were extracted from Survey Monkey software with rectification of discrepancies in the data analysis through a review of the original survey responses. In both surveys, the respondents provided answers concerning their location of practice, years of practice, and gender. We used chi-square tests to compare choices between the recommendation-for-patients group versus the recommendation-for-self group. We performed multinomial multivariable logistic regression analysis with choice of anti-VEGF agent as the dependent variable and recommendation-for-patient versus recommendation-for-self as the primary independent variable, but also including the three demographic variables as categorical covariates. We also performed a subsequent multinomial multivariable logistic regression analysis with treatment regimen as the dependent variable and recommendation-for-patient versus recommendation-for-self as the primary independent variable.

**Results**

A total of 226 of 800 physicians returned the questionnaire (response rate, 28.3%). The response rate and therefore the number of physician responders were equal in both groups. Demographic data concerning the respondents are shown in Table 1 and were compared between the groups using the chi-square test. There were no differences between the area of practice or gender of the 2 sets of respondents (P = 0.96, 0.60, 0.19).
respectively). A tendency for Scenario 2 respondents to have been in practice longer did not achieve statistical significance ($P = 0.081$).

As shown in Figure 1, the majority of physicians recommending a treatment to a hypothetical patient would choose bevacizumab (52.2%), with fewer choosing ranibizumab (27.4%) and aflibercept (20.4%). In contrast, among the group hypothetically prescribing for themselves, respondents’ percentages of choice of drug were approximately equal between choices of drugs. This difference in recommendation of bevacizumab for a patient (52.2%) versus self (32.7%) was statistically significant ($P = 0.011$). Multiple logistic regression analysis, adjusting for all three demographic variables confirmed that the odds of physicians selecting bevacizumab as opposed to aflibercept for patients were 2.82 times greater than when choosing it for themselves ($P = 0.003$), whereas the odds ratio of physicians selecting ranibizumab as opposed to aflibercept for patients was not significantly different from that of selecting it for themselves (OR = 1.48, $P = 0.30$).

The recommended drug was influenced by the geographical location of the physician (Table 2, $P = 0.005$). Respondents practicing in the Northeast chose each of the three drugs with approximately equal frequency, whereas those in other regions were most likely to select bevacizumab. The respondents’ scenario (patient vs. self) did not influence this association of choice with location ($P = 0.95$). The length of practice and gender of respondent did not influence the choice of drug ($P = 0.89, 0.12$, respectively).

As seen in Figure 2, there was a marked difference in the dosing regimen selected by the respondents to the 2 scenarios ($P = 0.004$). Only 2 of the group (2%) hypothetically treating patients selected monthly dosing compared with 28 selecting PRN (25%) and 83 selecting treat and extend (73%). However, 15 of the group (13%) hypothetically treating themselves selected monthly dosing compared with 27 (24%) and 71 (63%) selecting PRN and treat and extend, respectively. None of the three demographic variables influenced the choice of dosing regimen (all $P > 0.35$), and there were no interactions between any of the demographic variables and scenario (patient vs. self) with respect to the choice of dosing regimen. Multiple logistic regression analysis, adjusting for all three demographic variables,

<table>
<thead>
<tr>
<th>Table 1. Respondent Characteristics</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Area of practice*</td>
</tr>
<tr>
<td>Northeast</td>
</tr>
<tr>
<td>South</td>
</tr>
<tr>
<td>Midwest</td>
</tr>
<tr>
<td>West Coast</td>
</tr>
<tr>
<td>Years of practice**</td>
</tr>
<tr>
<td>0–10 years</td>
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<tr>
<td>10–20 years</td>
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<tr>
<td>20–30 years</td>
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<tr>
<td>30–40 years</td>
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<tr>
<td>Gender***</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
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</tbody>
</table>

*$P = 0.96$, **$P = 0.081$, ***$P = 0.60$.

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confirmed that the odds ratio of physicians selecting monthly dosing as opposed to treat and extend for themselves were 8.55 times greater than when they were choosing for patients ($P = 0.006$).

**Discussion**

This study demonstrates that retina specialists differ in their treatment recommendations for a hypothetical patient in comparison with treatment for themselves in a similar situation. Most retina specialists would choose bevacizumab when treating a patient, but are essentially equally divided between bevacizumab, ranibizumab, and aflibercept when treating themselves. The contrast suggests the presence of bias and discordant weighing of potential treatment outcomes.

There are a variety of considerations when recommending a treatment, such as patient financial responsibility, practice reimbursement issues, and efficacy and safety of a therapy. The results indicate that the geographical location of practice may also influence a treatment recommendation. Recent census data cite that more people are uninsured in the south and west in comparison with the northeast (18.6% and 17%, respectively, vs. 11%). The disparity in health care coverage between geographical regions may influence the choice for a more economical treatment such as bevacizumab. Other factors, such as area-specific preferred practice or payer requirements, may also influence the treatment preference.

The variation between the study groups could stem from the cost difference of these therapeutic regimens. Ranibizumab is estimated to cost up to $23,400 per year for a monthly dosing regimen, and aflibercept can incur costs up to $14,800 per year (8 doses per year). However, bevacizumab is estimated to only cost $595 per year for a monthly dosing regimen. More specifically, most patients requiring anti-VEGF treatments are more likely to be under Medicare coverage, and co-payments for Medicare patients per intravitreal injection range from $11.22 for bevacizumab to as high as $406.09 for ranibizumab. Because of the higher cost of ranibizumab and aflibercept when compared with bevacizumab, physicians may be more inclined to recommend the more economical option for their patients, given clinical trial data that indicate little difference in outcomes between the therapeutics. In contrast, physicians may prefer treatment with ranibizumab or aflibercept because the safety profile, Food and Drug Administration approval status, and the ability to obtain the drug from sources other than a compounding pharmacy. Physicians are also more likely to have more comprehensive insurance coverage than the general population and the income to

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**Table 2. Physician Recommendations Stratified by Geographic Locations**

<table>
<thead>
<tr>
<th>Geographic Location</th>
<th>Aflibercept, n (%)</th>
<th>Bevacizumab, n (%)</th>
<th>Ranibizumab, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>30 (30)</td>
<td>33 (33)</td>
<td>38 (38)</td>
</tr>
<tr>
<td>South</td>
<td>11 (21)</td>
<td>23 (44)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Midwest</td>
<td>19 (35)</td>
<td>28 (52)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>West</td>
<td>2 (11)</td>
<td>123 (68)</td>
<td>4 (21)</td>
</tr>
</tbody>
</table>

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![Fig. 2. Physicians differ in their selection of dosing regimens when treating a hypothetical patient compared with treating themselves in a similar situation. However, most of the physicians in both groups chose the treat and extend regimen for both themselves and a hypothetical patient.](image-url)
supplement costs of the treatments not covered by insurance. These economic factors can weigh heavily in a physician’s treatment recommendation and may have been key factors in the discrepancies for treatment recommendations for the patient or for the physicians themselves.

Afibercept was the least chosen pharmaceutical when recommending treatments for their patients; however, it was the most likely choice for physicians when recommending treatments for themselves. Afibercept is a relatively new biologic for treatment of exudative AMD. Previous evidence indicating that physicians prefer familiar treatment options compared with unfamiliar lower cost options may explain why retina specialists are less likely to recommend afibercept, a newer and less expensive therapeutic, to their patients with exudative AMD. Prospective clinical data demonstrates a similar efficacy and safety profile between ranibizumab and afibercept, and there is a dosing advantage to afibercept in their registration trials. In addition, anecdotal data suggest that afibercept may have some efficacy advantages in anatomical outcomes. Furthermore, theoretical models demonstrate that afibercept has a longer half-life than other anti-VEGF treatments. These factors may motivate physicians to choose afibercept for themselves.

There was a marked difference in the dosing regimen selected by the respondents to the two scenarios where the odds ratios of physicians selecting monthly dosing as opposed to treat and extend for themselves were 8.55 times greater than when they were choosing for patients \( P = 0.006 \). This may imply that physicians prefer a more conservative approach to their own disease management than for their patient population as a whole.

Our study has several limitations. First, our hypothetical patient is a 70-year-old patient, but most of our physician respondents, in both the self-recommendation and patient recommendation groups, are much younger. The difference in age may bias the treatment choice and management decisions of the surveyed physicians. However, since our study groups were randomized by location and balanced with respect to years of practice, any bias with respect to age should be equally distributed between the groups.

Another limitation lies in the fact that surveys are susceptible to nonrespondent bias. We assume that disinterest, spam filtering, and prioritization of tasks reduced the rate of response. However, our response rate was nevertheless high enough to power our study and demonstrate significant results between the two groups. Although our response rate was relatively low, it was identical between the two study groups, minimizing the effect of nonrespondent bias. Because we conducted a randomized survey, we can conclude that these results reflect true differences in physician recommendations rather than differences as a result of chance.

In conclusion, our study demonstrates that when considering cases of exudative AMD, physicians would recommend different treatments for themselves than they would for a patient. Future treatment for exudative AMD may benefit from reconciling these differences by addressing gaps in research regarding efficacy and safety or developing payment plans for more expensive but perhaps desirable treatments.

**Key words:** afibercept, anti-VEGF therapy, bevacizumab, cognitive biases, exudative age-related macular degeneration, physician treatment preferences, ranibizumab, treatment choices for exudative AMD.

**Acknowledgments**

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**References**


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