Original Article

Patient adherence to therapy after switch to aflibercept from bevacizumab or ranibizumab for treatment-refractory neovascular age-related macular degeneration

Simon D Archambault[1,2], Megan M Nichols[1,2], James C McCullum[1,2], Yubo Zhang[1,3], Elise E Steinberger[1,2], David J Ramsey[1,2]

Purpose: Clinical trials have demonstrated that switching patients from intravitreal bevacizumab (IVB) or ranibizumab (IVR) to aflibercept (IVA) for treatment-refractory neovascular age-related macular degeneration (nAMD) can decrease the injection frequency. This study evaluated whether there was a difference in the rate of injections or nonadherent events after switching therapies. **Methods:** The study comprised a retrospective, cross-sectional analysis of patients treated for nAMD from 2010 to 2018 who received ≥3 intravitreal injections of IVB/IVR prior to switching to IVA because of treatment-refractory nAMD. The treatment index, outcomes, and adherence to treatment were compared between both treatment regimens. **Results:** Sixty-two patients (67 eyes) met inclusion criteria. There was no change in the treatment index (0.65 versus 0.66, P = 0.650) or the number of nonadherent events (33 versus 36, P = 0.760) after the switch from IVB/IVR to IVA. Central macular thickness (CMT) increased 7.7%±13.8% in eyes that had a nonadherent event (283±69 μm to 304±75 μm after resuming care, P = 0.039). There was no short-term impact on visual acuity (VA) for this subset of eyes (0.387±0.202 LogMAR versus 0.365±0.156 LogMAR, P = 0.636). Patients who had nonadherent events ended the study with similar VA compared with patients who had no treatment lapses (0.370±0.616 LogMAR versus 0.337±0.638 LogMAR, P = 0.843). **Conclusion:** Switching from IVB/ IVR to IVA for treatment-refractory nAMD in a real-world setting does not reduce the treatment index or increase adherence to treatment. Although there were short-term anatomical effects resulting from missed treatments, VA remained stable.

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Intravitreal injections of agents targeting anti-vascular endothelial growth factor (anti-VEGF) are the standard of care for treating neovascular age-related macular degeneration (nAMD). Clinical trials have demonstrated that regular injections stabilize the disease and preserve vision,[1-3] but patients often have difficulty maintaining the frequent injection protocols established by clinical trials. Treat-and-extend and *pro re nata* approaches reduce treatment burden for some patients, but refractory nAMD requires more frequent dosing, and inadequate adherence with prescribed treatment can lead to worse visual outcomes.[4-7]

Intravitreal aflibercept (IVA) was demonstrated to be noninferior to intravitreal bevacizumab (IVB) or intravitreal ranibizumab (IVR) in randomized clinical trials.[3,8] When treated in a highly controlled environment, patients required significantly fewer injections with IVA compared to IVR and IVB.[9-12] Whether IVA improves real-world adherence and reduces treatment frequency remains uncertain.

This study examined whether switching patients with refractory nAMD from treatment with IVB or IVR to IVA resulted in improved functional outcomes, reduced treatment burden, and enhanced adherence to recommended dosing intervals. In addition, patient-specific factors predictive of nonadherence were investigated.

Methods

This study was conducted in compliance with the tenets of the Declaration of Helsinki, and it received Research Ethics Board approval. Information was gathered and secured in compliance with the Health Insurance Portability and Accountability Act.

Study participants

This retrospective, cross-sectional study included patients diagnosed with and treated for nAMD between January

[1]Division of Ophthalmology, Department of Surgery, Lahey Hospital & Medical Center, 1 Essex Center Drive, Peabody, MA, [2]Department of Ophthalmology, Tufts University School of Medicine, Boston, MA, [3]Brandeis University, Waltham, MA, USA

Correspondence to: Dr. David J Ramsey, Lahey Medical Center, One Essex Center Drive, Peabody, MA 01960, USA. E-mail: David.J.Ramsey@lahey.org

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2010 and April 2018. All patients initially received treatment with IVB or IVR before transitioning to IVA because of treatment-refractory nAMD. All eyes were treated with an initial set of three-monthly loading doses of IVB or IVR, in accordance with a treat-and-extend protocol designed to sustain a fluid-free macula, as previously described.[13] Patients were switched to IVA when refractory to initial treatment, defined by the inability to attain or maintain a 28-day fluid-free period between treatments. Patients with other retinal conditions were excluded from the study (e.g. retinal vein occlusions, diabetic retinopathy, myopic choroidal neovascular membranes, or central serous retinopathy). Patients who initiated treatments before 2010 or received injections at outside institutions or failed to return to therapy after a nonadherent event were also excluded. No participant included in the study had any serious systemic or ocular adverse events reported.

Study design and protocol

Demographic and clinical data were extracted from patient electronic health records. Frequency of intravitreal injections, visual acuity (VA), optical coherence tomography (OCT) findings, and adherence to treatment were documented and compared among the different treatment regimens (IVB or IVR vs. IVA). The treatment index was determined by dividing the total number of intravitreal injections a patient received during the treatment period by the maximum potential number of injections for that period, as defined by a maximum injection frequency of one injection every 28 days, in accordance with the package insert.[14] The result was reported as a percentage, with 100% representing the maximum number of injections. Visual outcomes were assessed using best-recorded VA for all statistical analyses (i.e. using best-corrected VA, when available, followed by VA with correction, followed by uncorrected VA). Anatomic outcomes were assessed using central macular thickness (CMT) determined by means of OCT imaging. Treatment nonadherence was defined as a greater than 14-day delay in follow-up beyond the recommended return interval. Factors potentially related to nonadherence (age, sex, VA, CMT, distance from the eye clinic, type of insurance, or estimated household income) were assessed. Mean household income by zip code was determined by using 2018 US Census Data for total income divided by the number of returns for each zip code as an approximation for the measure.[15] The approximate distance to the clinic for each patient was computed by using an Excel VBA program to access Microsoft Maps, which calculated the number of miles between each patient's home and the clinic by zip code, as previously described.[16]

Statistical analysis

Data were encoded and analyzed using SPSS® Statistics version 28.0 (IBM Corp, Armonk, NY, USA). Snellen VA was converted to the logarithm of the minimum angle of resolution (LogMAR) for comparison. Data are presented as mean (±standard deviation [SD]) for continuous variables, frequency (count), and relative frequency (percentage) for categorical data. Student's *t*-test was used to compare normally distributed quantitative variables, while nonparametric Wilcoxon signed rank test was used for non-normally distributed quantitative variables. Pearson's correlation coefficient and Spearman rank correlation were used to evaluate the linear relationship between continuous and ordinal variables, respectively. All tests were 2-sided, and *P* values below 0.05 were regarded as statistically significant.

Results

Sixty-two patients (67 study eyes) with nAMD who received anti-VEGF injections between 2010 and 2018 met the criteria for inclusion in the study. The mean age of patients at the time of diagnosis of their first eye was 80.5 ± 6.8 years, and 61% were female [Table 1]. Eighty-four percent of patients were initiated on anti-VEGF therapy with IVB, while 16% of patients were initiated with IVR. Within a 14-month period after the treatment was initiated, half of the patients who were initially on IVB or IVR were transitioned to IVA, with the median time for the switch being 398 days [Fig. 1]. Patients were treated for an average of 3.9 ± 2.2 years. Eyes spent on an average 66% of total treatment on IVE, which accounted for 62% of injections received.

Patient adherence

A total of 21 patients had one or more nonadherence episodes in which the follow-up was >14 days beyond the recommended return in the period before the switch to IVA. After the switch to IVA, 18 patients had one or more delayed returns of >14 days ($\chi^2 = 0.3367$, $P = 0.562$). A total of 31 nonadherent events occurred in the period before patients switched to IVA and 35 occurred after the change in medication. There was a correlation between having at least one nonadherent event in the pre-switch period with one in the post-switch period ($r = 0.2768$, $P = 0.028$), and between the total number of such events in each period ($r = 0.4514$, $P < 0.001$). For this subset of patients who had nonadherent events, the total number of days spent beyond the recommended treatment interval was similar between the period before the switch to aflibercept and the period after the switch (42 ± 26 vs. 50 ± 50 days, $P = 0.492$). Nine out of the 30 patients who had a nonadherent event had at least one in both periods (30%), which is similar to the overall proportion of patients who had nonadherent

Table 1: Demographic data for the study population

Demographic variables	Mean (SD) or *n* (%)
Age, mean years (SD)	80.5 (6.8)
Sex, *n* (%)	
Female	38 (61)
Male	24 (39)
Race, *n* (%)	
White	60 (96)
African American	1 (2)
Hispanic	1 (2)
Type of insurance, *n* (%)	
Commercial	3 (5)
Medicare	59 (95)
English as a primary language, *n* (%)	62 (100)
Currently employed, *n* (%)	3 (5)
Distance to clinic from patient's home address, miles (SD)	11.6 (8.8)
Estimated household income, $ thousands (SD)	106 (34)

SD=standard deviation

events in the pre-switch period (34%; $\chi^2 = 0.1379$, $P = 0.710$) and post-switch period (26%; $\chi^2 = 0.0091$, $P = 0.924$). However, the time to the first nonadherent event after the switch to IVA was significantly later compared to the first nonadherent event that occurred in the period before the switch (326 ± 368 vs. 712 ± 579 days, $P = 0.018$). Neither the time to switch nor the number of intravitreal injections correlated with the risk of experiencing a nonadherent event in either period.

One patient experienced a nonadherent event just before switching to IVA treatment. The reasons for nonadherence were frequently not documented in the medical record. Recorded explanations for delayed follow-up included illness or hospitalization (n = 13), inclement weather (n = 3), and attendance at a funeral (n = 1).

Treatment frequency

Patients received an average of 12.0 ± 7.7 injections of IVB or IVR, followed by an average of 23.1 ± 14.9 IVA injections. This translated to an injection every 5.7 ± 1.2 weeks pre-switch, compared to one every 6.0 ± 1.9 weeks in the post-switch period ($P = 0.282$). However, the average injection interval immediately before the switch to IVA was 5.4 ± 1.5 weeks. After the switch, the average injection interval for IVA increased to 7.8 ± 3.6 weeks by the end of study ($P < 0.001$). Nearly half of the patients (45%) were able to extend their treatment interval by two or more weeks after switching to aflibercept.

The average treatment index was similar before (65.5%) and after (66.4%) the switch to IVA ($P = 0.651$). Unsurprisingly, those patients who had one or more nonadherent events had a lower average treatment index both before the switch to IVA (71% ±9.5% vs. 57% ±9.4%, $P < 0.001$) and after the switch to IVA (71% ±16% vs. 58% ±13%, $P < 0.001$). Finally, the subset of patients who had one or more nonadherent events spent a longer period out of compliance with recommended treatment in the pre-switch period (11% ±9.7%), compared to the post-switch period (5.4% ±4.5%, $P = 0.038$). This could be partially accounted for by the fact that a similar number of nonadherent events took place over a longer course of treatment. Finally, the treatment index was the only study variable that correlated with experiencing a nonadherent event ($r = -0.401$, $P < 0.001$).

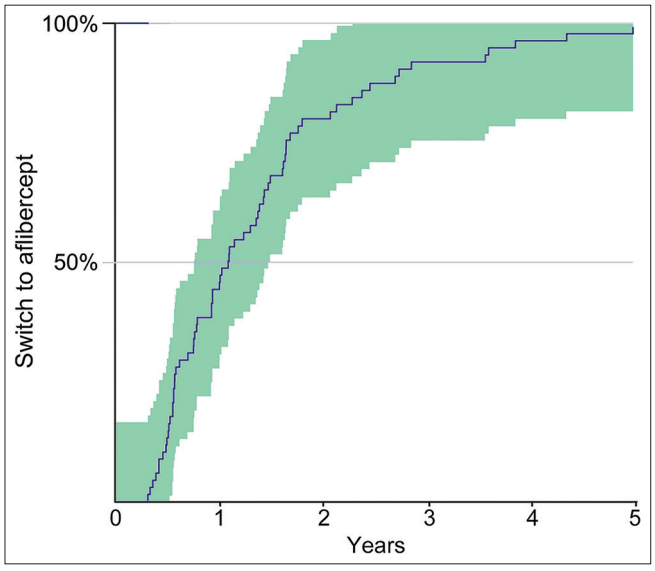

Figure 1: Time to switch from IVB or IVR to IVA. Fifty percent of patients switched to IVA in just over 1 year (T_{50} = 398 days [13 months]). IVA = intravitreal aflibercept, IVB = intravitreal bevacizumab, IVR = intravitreal ranibizumab

Visual and anatomical outcomes

VA did not significantly differ over the course of the study. Patients on average had similar VA at the initiation of IVB or IVR (LogMAR 0.361 ± 0.690), before initiation of IVA (LogMAR 0.347 ± 0.672), and at the end of the study period (LogMAR 0.333 ± 0.635). A prior nonadherent event did not impact VA at the time of the switch (LogMAR 0.448 ± 0.274 vs. 0.413 ± 0.332, $P = 0.704$). In the period after the switch to IVA, a nonadherent event caused a significant increase in CMT (283 ± 69 μm increasing to 304 ± 75 μm, a change of + 20.8 ± 38.8 μm or + 7.7% ±13.8%, $P = 0.039$; Fig. 2]. However, a similar trend was not observed in VA. VA before and immediately after a nonadherent event remained comparable, which indicated there was no short-term impact on VA among these patients (LogMAR 0.387 ± 0.202 vs. 0.365 ± 0.156, $P = 0.636$). An analysis of the impact of nonadherence on near-term visual and anatomical outcomes before the switch to IVA is limited due to a change in electronic medical record systems. Finally, there was no difference in vision at the end of follow-up between patients who had one or more delayed returns while on IVA compared to those who did not have any unplanned treatment interruptions (LogMAR 0.385 ± 0.217 versus 0.426 ± 0.311, $P = 0.617$). One patient was excluded from this analysis because that patient experienced a delay in treatment while undergoing cataract surgery in the eye treated for nAMD.

Discussion

The number of patients with age-related macular degeneration is predicted to increase because of the aging of the population.[17] When aflibercept and bevacizumab were initially compared,

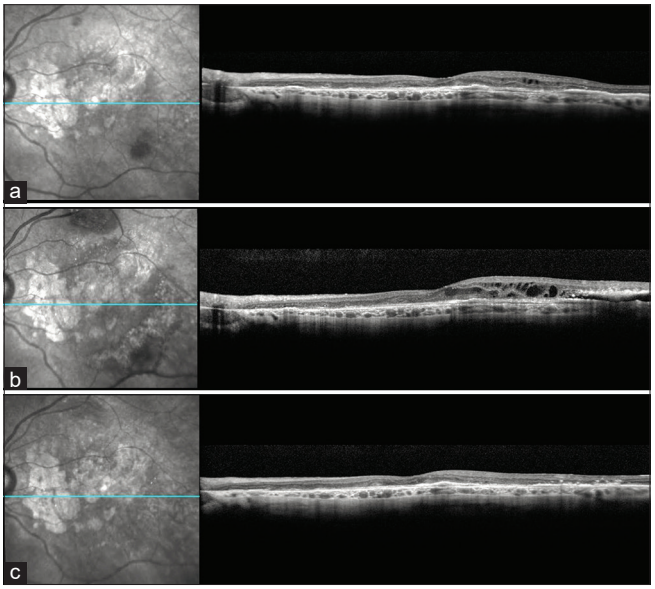

Figure 2: Impact of Nonadherent Event on Retinal OCT Imaging. (a) OCT scan obtained the visit before a nonadherent event. (b) OCT scan at the initial follow-up after the nonadherent event, showing increased CMT due to worsened exudation and retinal hemorrhage, confirmed clinically. (c) OCT scan after treatment resumed post nonadherent event. CMT = central macular thickness, OCT = optical coherence tomography

strict clinical trial protocols were in place to optimize patient compliance with treatment, including receiving the help of study coordinators, study-provided medications, and other incentives for participation.[3-19] However, patients undergoing treatment for nAMD must contend with real physical,[20,21] psychological,[6,20,22] and financial[23,24] burdens associated with treatment. These burdens can often influence a patient's ability to comply with recommended treatment protocols.

Several randomized clinical trials have demonstrated that IVA might potentially alleviate this burden by lengthening the injection interval without sacrificing visual or structural outcomes.[11,12] Although our study demonstrated real-world patterns align with the results observed in clinical trials,[25] such that almost half of patients in our study were able to extend their treatment intervals by 2 weeks or more compared to the period before switching, this finding did not reach statistical significance. This outcome likely reflects the fact that not all patients with treatment-resistant disease responded as favorably to the switch in agent. Although this trend did not reach statistical significance, it holds potential clinical relevance because of the possibility of fewer clinic visits and injections for certain patients. This, in turn, could alleviate the challenges associated with treatment, including the risk of complications tied to intravitreal injections.

In this study, all nonadherent patients eventually resumed their regular injection schedule, as those who did not return or sought care elsewhere were excluded from the analysis. Most patients had a lapse in care that only lasted approximately 6 weeks, and the majority of these lapses were caused by hospitalizations. Fortunately, these lapses led to only temporary anatomical changes that quickly reversed once therapy was resumed, with no noticeable long-term impact on VA. This finding raises questions about the true implications of transient nonadherence. Overall, our findings emphasize the importance of physicians exercising caution when making assumptions about the causes and consequences of treatment nonadherence. Chastising patients without allowing for underlying factors can potentially weaken the physician–patient relationship.[26] Therefore, health-care providers should approach nonadherence with an open and empathetic mindset, considering the various circumstances that may contribute to nonadherence. Nevertheless, extended treatment gaps pose a substantial risk of exacerbating nAMD and contribute to suboptimal disease management, which is associated with unfavorable visual outcomes.[27] It is important to note that this study's purpose was to describe trends and observations regarding temporary lapses in care and not to assess the merits or consequences of a treat-and-extend treatment protocol.[28]

Our study did not identify any significant trends in patient-related factors that substantially contributed to nonadherence. Previous studies have indicated that factors such as higher baseline VA, shorter distance to the hospital, higher education level, and elevated socioeconomic status are associated with improved patient adherence to treatment.[6] However, in our study, the treatment index was the only factor that correlated with nonadherence. Patients who required more frequent injections were less likely to experience nonadherent events. We propose that individuals requiring frequent injections might have been experiencing more pronounced visual symptoms or heightened concerns about vision loss. Such patients, along with their health-care providers, might have placed increased importance on attending regular injection appointments to mitigate disease progression. Conversely, patients who maintained stable vision and retinal anatomy would have been more likely to extend injection intervals. This group might have attributed less urgency to attending injection visits, thereby increasing the likelihood of nonadherence.

The present study is subject to several limitations. The small sample size resulting from strict inclusion and exclusion criteria limits the overall statistical power of the study. A larger dataset would be beneficial in identifying potential trends in patient-related factors contributing to nonadherent events. It is important to note that our study population was derived from a suburban, academic medical center, where the majority of patients were older, identified as White, and the vast majority were insured by Medicare, a government-provided benefit linked to age. This homogeneity may limit the generalizability of our findings to a more diverse and less well-insured population. Future studies should ideally examine a broader spectrum of patients, including those with varying types of insurance that could influence the financial impact of treatment or its associated costs. Another limitation of our study is its exclusion of patients who discontinued treatment, including those who did so before the opportunity to switch to IVA arose. In addition, the patients in our study had a significantly longer treatment duration with IVA, compared to IVB or IVR. That factor could potentially lower the treatment index by providing more opportunities for nonadherent events or treatment failure. We also did not examine the adherence pattern in patients who did not develop treatment-refractory nAMD. Furthermore, due to variations in clinical documentation and limitations imposed by the electronic medical record system and data archiving, CMT was not available for all patients at the beginning of treatment. In addition, it was not feasible to subclassify consistently the type of activity present in all scans throughout the entire study period, such as identifying the presence of intraretinal or subretinal fluid. Future studies should explore those biomarkers in more depth and detail. Lastly, our study focused solely on patient visits before the onset of the coronavirus disease 2019 (COVID-19) pandemic. This period saw a substantial impact on patient adherence to intravitreal injection treatment, which was associated with worse anatomical outcomes.[29,30] Future studies should explore the long-term impact of COVID-19 on treatment frequency and adherence in nAMD.

Conclusion

In conclusion, our study determined that transitioning from IVB or IVR to IVA for treatment-refractory nAMD did not lead to a decrease in treatment index or enhanced treatment adherence. However, in a real-world clinical setting, despite short-term anatomical effects from missed treatments, VA remained stable. Future studies should focus on investigating the effects of various treatment strategies and newer medications on patients' treatment adherence and their potential to achieve positive long-term visual outcomes.

Availability of data and materials: The datasets generated and analyzed during the current study are not publicly available due to the utilization of confidential patient medical record data. Participants in this study did not authorize their data to be shared publicly; consequently, supporting data is not available for public access.

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Abbreviations or Acronyms

IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVA, intravitreal aflibercept; OCT, optical coherence tomography; VA, visual acuity, LogMAR, logarithm of the minimum angle of resolution; SD, standard deviation; COVID-19, coronavirus disease 2019; SD, standard deviation

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Conflicts of interest

There are no conflicts of interest.

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