Is There a Dose-Response Relationship?
Real-World Outcomes of Anti-Vascular Endothelial Growth Factor Treatment in Neovascular Age-Related Macular Degeneration

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Anti-vascular endothelial growth factor · Treatment · Response · Prediction · Neovascular age-related macular degeneration

Abstract
Purpose: The aim of study was to explore the dose-response relationship of anti-vascular endothelial growth factor (VEGF) agents, with bevacizumab as 1st-line treatment, on the visual-acuity (VA) outcome during the first year of treatment in neovascular AMD (nAMD) patients in real-life conditions. Methods: This was a retrospective, observational, single-center study at the Ophthalmology Division, Tel Aviv Medical Center. Inclusion criterion was naive AMD patients treated with anti-VEGF injections between the years 2017–2020. Electronic medical records were scanned using the MDClone software, and data from time of diagnosis, containing baseline VA, final VA, number of injections, and the injected agent, were gathered. Subjects were divided into three groups based on their baseline VA (“good,” “middle,” and “low”). Results: A total of 672 patients were included. The cohort demonstrated a statistically nonsignificant correlation with a positive trend between the log transformation of the number of annual injections and the change in VA (p = 0.145). However, a significant correlation was established within the “low-VA” group (p = 0.015). The “good-“ and “middle-VA” groups did not reach statistical significance. Baseline VA was the single significant predictor for VA gain within patients with baseline VA of 6/12 or less. Conclusions: A dose-response relationship between anti-VEGF injections and the VA outcome was found only for patients with low baseline VA. Individual patient characteristics might need to be taken into account to customize treatment regimen and improve visual outcome.

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in elderly people in developed countries [1]. AMD prevalence worldwide, within the age of 55–85 years, is estimated to be 8.7%, with neovascular AMD (nAMD) being 10–15% of cases [2, 3]. nAMD treatment has been revolutionized with the introduction of intravitreal anti-vascular endothelial growth factor
(VEGF) injections. Pivotal randomized control trials (RCTs) used monthly dosing regimens and proved safety and efficacy of anti-VEGF agents by improvement of retinal anatomy and preservation of vision [4, 5]. Due to treatment burden to patients, caregivers, and health systems, in addition to the accumulative risk for endophthalmitis each injection carries, alternate strategies such as pro re nata (PRN) or treat-and-extend (TE) protocols have been introduced, and these have been shown to be non-inferior to monthly dosing regimens [6–9]. While PRN and TE regimens have become common clinical practice, observational clinical studies such as AURA and LUMINOUS revealed disappointing real-life global data regarding outcomes of anti-VEGF therapy in nAMD patients [10, 11], clearly inferior to those reported in RCTs which used the same treatment strategies. This discrepancy was mainly attributed to lower injection frequency comparing to clinical trials.

A recent PubMed and Cochrane Systematic Review conducted by Spaide [12] demonstrated that there was a “dose-response characteristic” of ranibizumab and aflibercept (not bevacizumab) injections and visual-acuity (VA) change during the first year of treatment for nAMD. A total of 96 articles, including observational studies with vary treatment strategies, were included. Given the number of injections in each study, the “dose” was defined as Log of the number of annual injections in each study, whereas response was defined as VA change from baseline. Remarkably, after accounting for the number of injections, neither the specific anti-VEGF agent used nor the treatment strategy was significant in predicating VA changes.

The purpose of our current study was to explore the dose-response relationship of anti-VEGF agents on the VA outcome during the first year of treatment, using raw real-life data, extracted from individual nAMD patients’ electronic medical records (EMR) in a tertiary medical center, with bevacizumab being first-line treatment and the main agent. This novel approach to analyze nAMD data might shed light on the common variability of different treatment strategies and their efficacy for the specific patient.

### Materials and Methods

We conducted a retrospective, observational, single-center study at the Ophthalmology Division, Tel Aviv Medical Center (TLVMC). Institutional Review Board (IRB) approval was obtained. The research adhered to the tenets of the Declaration of Helsinki. Patients’ EMRs seen in the Retina Unit between January 1, 2017, to December 31, 2020, were scanned for nAMD patients
treated with anti-VEGF injections using the MDClone, a data extraction and synthetization platform which provides patient-level data around an index event (https://www.mdclone.com/), previously used in several recent studies [13, 14]. This study used de-identified, original, nonsynthesized, EMR data.

Database and Study Population

The protocol for treating nAMD patients at the TLVMC consists of a loading dose of at least 3 monthly intravitreal bevacizumab injections, followed by a TE or PRN regimen based on VA and OCT analysis. Bevacizumab is the first line of funded treatment in Israel for nAMD. In case of insufficient response, which is defined as less than 20% reduction in CMT or worsening vision after at least 3 monthly bevacizumab injections, the patient is eligible to switch to alternative anti-VEGF treatment such as aflibercept or ranibizumab, at the discretion of the treating retina specialist.

To be included in the analysis, patient records had to fulfill the following inclusion criteria: (1) diagnosis of nAMD; (2) treated with at least 3 monthly anti-VEGF injections which were administered within the first 4 months from diagnosis; (3) 12-month follow-up data from time of diagnosis containing baseline VA, final VA, number of injections, and the injected anti-VEGF agent. Three groups of patients were defined, according to their baseline VA:

- **good VA** ≤0.3 logMAR (6/12 or better),
- **low VA** ≥1 logMAR (6/60 or worse), and
- **middle VA** for all remaining patients in between.

VA was measured using the Snellen chart. For statistical analysis and calculation of VA change, a transformation to logMAR was conducted where a logMAR change of 0.3 was equated to 3 lines change [12].

Outcome Measures

The main outcome measure was the correlation between injection frequency and VA changes from baseline to month 12. Secondary-outcome measures included proportion of patients who (1) maintained stable VA (±0.1 logMAR), (2) who had a significant VA gain or (3) VA loss (± 0.2 logMAR), (4) correlations between VA change and baseline VA, (5) VA change, and patient age.

Statistical Analysis

Only one eye of each patient was included in the study, agreeing that the right eye is the default eye in case both eyes were eligible according to inclusion criteria. Results are expressed as mean ± SD, median (range), or N (%). For the comparison of continuous and categorical data at final visit versus baseline, the paired t test and McNemar’s test were used, respectively. For the comparison of continuous and categorical data between non-paired groups, the Student T and χ2 test were used, respectively.

A scatter plot and a trend line were used to visualize the correlation. Data were analyzed using Pearson’s correlation test among all variables and multiple linear regressions. All analysis and calculation were performed using IBM SPSS version 27 (IBM, Armonk, NY), whereas p value <0.05 was considered statistically significant.

Results

A total of 672 eyes of 672 patients were included in the study. Mean age was 80 years (±9.3, 47–107), with 58% female patients. The injected drug was 1.25 mg bevacizumab (Avastin) in 100% of patients for the first 3 injections and 81% of total injections. The remaining 19% divided between second-line treatments: 2.0 mg aflibercept (Eylea) in 9.1% and 0.5 mg ranibizumab (Lucentis) in 9.9% of total injections. The mean injection number during the 12-month study period was 6.4 ± 3.1 [3–12]. Mean baseline VA was 0.73 ± 0.6 logMAR (6/30); 211 (31%) patients had good VA, 293 (44%) had middle VA, and 168 (25%) had low baseline VA (Table 1).

Visual Outcomes

Final mean VA at month 12 was 0.72 ± 0.6 logMAR (6/30); 386 patients (57.5%) maintained stable vision, 134 (19.9%) gained two or more lines in VA, whereas 152 (22.6%) lost two or more lines in VA. Within the "good-VA" group, 162 patients (76.7%) maintained good VA (6/12 or better); from the remaining 49 patients (23.3%),
31 (14.7%) experienced a VA decline of ≥2 lines. In the “middle-VA” group, 68 patients (23.2%) maintained stable vision, 87 (29.7%) gained vision of ≥2 lines, and 64 (21.8%) lost 2 lines or more. In the “low-VA” group, 50 patients (29.7%) remained stable, while 64 (38%) had a VA improvement of ≥2 lines, and 32 (19%) had a VA loss of ≥2 lines (Fig. 1).

**Fig. 2. a–c** VA change as function of the log number of injections. A positive, nonsignificant trend of 0.39 and 2.34 was found within the “good-VA” (a) and “middle-VA” (b) groups, respectively. Within the “low-VA” group, a positive significant correlation of 7.63 was found (c).
Patients received a mean injection number of 6.5 ± 3.2, 6.7 ± 3.2, and 5.7 ± 3.1 in the “good-VA,” “middle-VA,” and “low-VA” groups, respectively (p = 0.004, Table 1). The proportions of patients who were switched to a second-line anti-VEGF agent were 48 (22.8%), 83 (28.8%), and 26 (9.6%) in the “good-VA,” “middle-VA,” and “low-VA” groups, respectively (p = 0.003).

We identified a positive correlation between the log transformation of the injection number and the change in VA for patients within the “good-VA” and “middle-VA” groups and for the whole cohort, although this did not reach statistical significance (p = 0.145). In contrary, patients with “low VA” reached statistically significant better VA outcomes when they received more injections (p = 0.015). This was expressed as a linear relationship between the log transformation of the number of annual injections and VA gain; Figure 2a–c). The following linear equation represents the expected improvements in VA in letters as a function of the annual number of injections within the “low-VA” group:

Letters of improvement = \(-5.32 + 7.63 \times \log(\text{number of injections})\)

To explore additional correlations to delta VA within the low-VA group, we calculated a multivariable regression containing age and baseline VA as independent variables in addition to log number of injections (Table 2). The R square was 0.17, with significant correlation for baseline VA (0.5 ± 0.1, p < 0.01) and patient’s age (0.009 ± 0.004, p = 0.017), while log number of injections was statistically significant as a given (−0.2 ± 0.05, p < 0.01). As an example, this means that the final VA would be expected to improve equivalent to a gain of 0.8 letters when increasing the number of annual injections from 5 to 6.

Linear regression analysis on the “middle-VA” group demonstrated statistical significance only for baseline VA (−0.4 ± 0.11, p < 0.01). In the “good-VA” group, no significant betas were observed.

Discussion

This real-world study on a large cohort of 672 nAMD patients investigated the correlation between the number of injections and the change in VA during the first year of treatment. While there was no significant correlation within the total cohort, we found a significant correlation among patients with baseline VA of 6/60 or less. In these patients, there was a linear relationship with statistically significant correlation between the log transformation of the number of injections and the mean VA gain. In addition, worse baseline VA and younger patient age were identified as significant predictors. Baseline VA was the single significant predictor for VA gain within all patients with baseline VA of 6/12 or less.

Lately, Spaide [12] demonstrated a linear relationship between anti-VEGF injections frequency and VA change during the first year of treatment, based on data from 96 RCTs and observational studies, containing different treatment regimens using ranibizumab and aflibercept. The report demonstrated a linear relationship with statistically significant correlation between the log transformation of the number of injections and the mean VA change, suggesting that, for example, 4 injections during the first year of treatment would lead to an estimated improvement of 3 letters in VA. The exclusiveness of the review study relied on the diverse data it contains, including a wide variety of studies, large patient population, and pa-

| Variable   | Multivariable analysis, β ± SD | 95% CI for odds | p values |
|------------|--------------------------------|----------------|----------|
| Low VA     |                                |                |          |
| Age        | 0.009±0.004                    | (0.002, 0.017) | 0.017    |
| VA at baseline | −0.508±0.111             | (−0.727, −0.289) | <0.01   |
| Log nr of injections | −0.204±0.057             | (−0.317, −0.091) | <0.01   |
| Middle VA  |                                |                |          |
| Age        | 0.006±0.003                    | (−0.001, 0.011) | 0.058    |
| VA at baseline | −0.396±0.114             | (−0.593, −0.145) | 0.001    |
| Log nr of injections | −0.056±0.040            | (−0.134, 0.022) | 0.158    |
| Good VA    |                                |                |          |
| Age        | 0.0001±0.002                   | (−0.004, 0.004) | 0.905    |
| VA at baseline | −0.105±0.405               | (−0.904, 0.694) | 0.795    |
| Log nr of injections | −0.008±0.029            | (−0.066, 0.05) | 0.787    |

CI, confidence interval; SD, standard deviation; VA, visual acuity.

Table 2. Multivariable regression analysis for change in VA at month 12
patients’ variance. Calculations were made on aggregated groups of patients from the different studies.

Therefore, the purpose of our current study was to test whether this mathematical relationship between log transformation of treatment frequency and delta VA could be regenerated by using real-world raw data of nAMD patients treated mainly with bevacizumab. One of the strengths of our study is the addition of information regarding baseline VA. The division of the patient cohort into three groups according to baseline vision allowed us to investigate correlations for each, separately. A significant correlation between the log transformation of the number of injections and VA gain was demonstrated only in patients with baseline VA of 6/60 or worse, and a linear relationship equation was extracted. In the “middle-” and “good-VA” groups, this correlation seemed to be insignificant. Different from RCTs, we did not apply exclusion criteria for baseline VA. Those results are aligned with a recent real-world study [15], based on private-practices aggregated data, which also established a linear relationship between the number of anti-VEGF injections and VA outcome and showed that patients with worse baseline VA tend to receive less injections in real-world conditions. Thus, although patients with worse baseline VA have a significant chance of improvement with each additional injection, as we demonstrated, they actually get less injections which makes them prone to under-treatment. This presents another advantage on real-life data, adding important information about patients with particularly good VA (>6/9) and low vision (<6/60). Implementation of these conclusions among patients with poor baseline VA – which are excluded from most studies – might be of great value for treating physicians.

Another additive value of our study is the data about use of bevacizumab as the 1st-line anti-VEGF drug, as mandatory in Israel, compared to the studies included by Spaide [12] using ranibizumab or aflibercept. According to the PAT Survey, 70% of retina specialists choose bevacizumab as 1st-line treatment [16].

In the current study, we analyzed raw individual’s data, in contrast to aggregated study data [12], where the mean change in VA for a similarly treated group of patients was predicted as a function of the number of annual injections, and each data point represented a group of patients from the same study, rather than individual patients. This methodological difference might offer an explanation for the discrepancy in our findings. Deepening the resolution into the single-patient level might add valuable information for treating physicians.

In the current study, 81.1% (545/672) of patients remained having stable vision or improved by ≥2 lines at month 12 (Fig. 1), which is in line with previous real-world observational studies [17]. Baseline VA was discovered as a significant predictor for VA gains among patients with VA ≤6/12, which is in line with the global LUMINOUS [10] and LUMIERE [18] studies. One explanation may be the “ceiling effect,” whereby patients with lower baseline VA have a larger potential for vision gain compared to those with high baseline VA.

Patients in our study received a mean number of 6.41 + 3.16 injections over 12 months. This number is only slightly below the mean number of injections given in the as-needed groups in the CATT [19] study (6.9 ± 3.0 for ranibizumab; 7.7 ± 3.5 for bevacizumab) and 7 in the IVAN [20] study. Compared to RCTs using a TE regimen, the number of injections given in our study was close to the ALTAIR [6] study (7.2 ± 0.9 and 6.9 ± 1.0 aflibercept) and below the frequency in the TREND [21] Study (8.9 ± 2.56). Real-world studies described similar numbers of injections during the first year of treatment with similar visual outcomes, in line with the findings in our current study [22].

Specifically, we showed the impact each additional injection has on the final VA within the “low-VA” group. For instance, adding a 6th injection (while the mean number of injections is 5.73 ± 3.08) will result in additional gain of 0.8 letter comparing to the VA achieved with 5 annual injections, which further emphasizes the importance of treatment for those patients, mostly excluded from RCTs.

The main limitation of our study is the lack of anatomical data. In our cohort, 152/672 patients (22.6%) lost ≥2 lines in VA. Macular scarring and atrophy are the main reasons for vision loss in nAMD [23]. The proportion of patients who developed scarring or subfoveal atrophy in our cohort is unknown. There is strong evidence that the presence of fluid in different compartments at baseline is predictive of the VA outcome in nAMD. While subretinal fluid at baseline has been shown to be a biomarker for greater visual gains, the presence of intraretinal fluid at baseline was correlated with worse baseline VA and a worse visual outcome [24–26]. Moreover, fluid status at baseline has been found to impact the need for re-treatment [27]. The lack of anatomical data raises a doubt regarding patients with low number of injections, who might have been undertreated or had a lower need for additional treatments based on OCT findings.

One more limitation is that in a real-world setting, although the common regimen of treatment in our center...
is T&E, the specific treatment regimen is not always documented specifically, thus neglecting the difference between T&E and PRN regimens. Additionally, VA measurements are not always performed under standardized luminance and with refraction, potentially leading to sub-optimal results compared to clinical trial settings [28].

We chose a study period of 12 months, to compare our real-world dataset to published accumulative data [12] on the same timeline. RCTs and real-world studies with long-term follow-up have shown VA decline. Investigation of the relationship between dose frequency and visual outcomes over years might add important information.

To conclude, we found a mathematical relationship between dose frequency and VA change during the 1st year of nAMD treatment only for patients with baseline VA of 6/60 or less. Baseline VA was a significant predictor for the VA outcome for patients with baseline VA of 6/12 or less. Annual injection dosage seems to explain only a small part of patients’ variance. Other factors, such as evaluation of retinal fluid dynamics, may need to be taken into consideration in order to pave the road for the optimal treatment regimen. New longer acting anti-VEGF agents might play an important role in reducing treatment burden while improving visual results.

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Statement of Ethics

As this was a retrospective study, participants' informed consent was not needed, in compliance with the Institutional Review Board (IRB) approval. This study protocol was reviewed and approved by IRB at the Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, approval number (0340-20). The research adhered to the tenets of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

Reut Shor, Adiel Barak, Marganit Shahar-Gonen, and Dinah Zur: substantial contributions to the conception or design of the work and the acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Anat Loewenstein and Michaella Goldstein: substantial contributions to the interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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