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Delta Injection Index as a Predictor of Visual Acuity Outcomes in Neovascular AMD patients in a Large Cohort with Long Term Follow-up

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ABSTRACT

Purpose: To investigate the change in Visual acuity (VA) of neovascular Age-related macular degeneration (nAMD) patients throughout three years of follow-up, according to the change in the number of annual anti vascular endothelial growth factor (VEGF) injections.

Methods: A retrospective, observational study of nAMD patients who were followed up between 06/2015-12/2021. Patients were divided into three groups based on the delta in the number of injections from baseline: no-delta, mid-delta, and high-delta.

Results: A total of 1,144 patients up met the inclusion criteria and were included in this study. Two hundred and twenty-six eyes were classified for the no-delta injections index group while 475 and 443 eyes were in the mid and high groups, respectively. Number of injections in the first year was similar between all three groups with 6.8±2.3, 7.1±2.0, and 6.9±2.5 for the no-delta, mid-delta, and high-delta group (p=0.345). Baseline VA was similar between all groups, 0.37±0.31, 0.39±0.31, and 0.41±0.34 (p=0.115), respectively. Final VA was significantly better for the no-delta group (p=0.035), as the mid-delta and high-delta injection index groups suffered statistically significant decline in VA throughout three years down to 0.59±0.46, and 0.61±0.50, respectively (p<0.01), while the no-delta patients experienced only a non-statistically significant decline in their VA to 0.50±0.41 (p=0.051).

Conclusion: Delta from baseline of annual anti-VEGF injections for nAMD patients may lead to less favorable visual outcomes with a statistically significant decline in visual acuity for the mid-delta and high delta groups in comparison to the no-delta group.

Key Words: Anti-VEGF; injection index; delta; nAMD; visual acuity

INTRODUCTION

Age-related macular degeneration (AMD) is an acquired degeneration of the outer retina that may lead to impairment of central vision among the elderly worldwide.(1–3) AMD is known for its progression over time, but the exact pathophysiology is yet to be fully understood.(4)

Visual impairment is caused mainly in neovascular AMD (nAMD) by neovascular membrane formation and the accumulation of fluid in and under the retina. Current treatment for nAMD include intra-vitreal injections of five anti Vascular endothelial growth factor (VEGF) agents: Bevacizumab, Ranibizumab, Aflibercept, Brolucizumab and Faricimab.(5–7) There are three main treatment protocols for anti-VEGF agents in nAMD: monthly fixed regimen, that is associated with the best visual outcomes (8,9) but also carries high burden for both patients and the health systems,(10,11) Pro-Re-Nata (PRN) protocol, in which the treatment is on an as-needed basis, and Treat-and-Extend (T&E) protocol, in which the interval between injections is extended up to 16 weeks, according to the patient's response for the treatment.(12)

Whether a change in the number of annual anti-VEGF injections given over years of treatment has by itself an impact on final visual acuity (VA) of patients, regardless of the chosen regimen, is unclear. Different studies have previously suggested that frequent injections and follow-up may lead to better visual acuity,(13–15) but they were mainly focused on the differences between the treatment protocols or the gap between follow-ups.

The purpose of this study is to investigate the change in VA of nAMD patients throughout three years of follow-up, according to the change (delta), in the number of annual anti-VEGF injections.

MATERIALS AND METHODS

This is a retrospective, observational study of patients with nAMD seen by retina specialists from June 10, 2015, to December 30, 2021, at the ophthalmology departments of Meir Medical Center, Kfar Saba and Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. The study was approved by the hospital institutional review board (IRB) of Tel Aviv Sourasky Medical Center and Meir medical center, Kfar Saba, (reference ID: TLV-1039-20) and was performed according to the tenets of the declaration of Helsinki.

Patients were identified by electronic medical records (EMR) of each department. Inclusion criteria included diagnosis of nAMD and treatment with intravitreal injections of anti VEGF agents for at least four consecutive years. Exclusion criteria included history of other macular diseases, such as diabetic retinopathy, retinal vein occlusion, retinal artery occlusion, central serous chorioretinopathy, and macular telangiectasia (MacTel). An additional exclusion criterion was the presence of vitreoretinal or optic nerve disorders, including retinal detachment, macular hole, optic neuropathy, retinal dystrophies and previous endophthalmitis. The data from the medical record of each patient was obtained and included age, gender, baseline VA, final VA and number and date of each injection.

Since the variance between eyes is usually less than that between subjects, the overall variance of a sample of measurements combined from both eyes is likely to underestimate the true variance.(16) Therefore, if both eyes met the inclusion criteria, one eye was randomly selected.

Best-corrected visual acuity (BCVA) was recorded and reported in Snellen fraction, which was converted into logarithm of the minimal angle of resolution (logMAR) values for statistical analysis.

In order to exclude the effect of anti VEGF agents on naïve patients, we included only patients with previous treatment of anti-VEGF injections for a period of 1 year prior to the study period. Then, we examined the number of injections of each patient in each year (injection index (17)) for the three years of follow up and subsequently divided the patients into three groups based on the delta in the number of injections in the last two years: First Group – No-delta: number of injections for the following 2 years was same as the first year of follow up; Second Group – Mid-delta: number of injections of the second year of follow up was 1 injection below baseline and 1-2 injections below the first year of follow up for the third year of follow up; And the third group – high-delta: number of injections of each year was 2 or more injections below the first year of follow up.

Statistical Analysis

All data collected in the study were entered into an electronic database via Microsoft Excel 2013 (Microsoft Corporation). Statistical analyses were performed using Minitab Software, version 17 (Minitab Inc, State College, PA). The 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 nonpaired groups, the Student T-test and chi-square test were used, respectively. A P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 1,144 eyes of 1,144 patients with three years of follow up met the inclusion criteria and were included in this study. Two hundred and twenty-six eyes were classified for the no-delta injections index group while 475 and 443 eyes were in the mid and high delta injection index groups, respectively. Fifty-seven precents of the patients were women and the mean age was 80 years old, with no statistically significant difference between the patients in the different groups in comparison of age, gender, and baseline VA (p=0.176, 0.995, and 0.115, respectively).
The demographics are presented in *Table 1*.

The number of injections in the first year of follow-up was similar between all three groups, patients received an average number of 6.8, 7.1 and 6.9 injections in the no-delta, mid, and high delta injection index groups, respectively. However, the average number of injections was significantly different between the groups in the second and third year. At the third year, while the average number of injections was 6.8 ±2.5 for the no delta injection rate group, it was 5.5±2.5 for the mid delta injection group and 4.1±2.7 for the high delta injection rate group (p<0.01).
Table 2 depicts the mean number of Intravitreal anti-VEGF injections per year.

Baseline VA was similar between all three groups and was 0.37±0.31 logMar VA for the no delta injection index group, 0.39±0.31 for the mid delta group and 0.41±0.34 for the high delta group (p=0.115). In the no delta injection index group, VA did not differ statistically between baseline and the final VA after three years and was 0.37±0.31 and 0.50±0.41 logMar VA, respectively (p=0.051). However, second and third year VA declined significantly in the mid and high delta injection index: for the mid delta injection index group, final VA decreased from 0.39±0.31 logMar VA in baseline to 0.59±0.46 in the third year (p<0.01); and as for the high delta injection index group, the Visual acuity decreased from 0.41±0.34 in baseline to 0.61±0.50 in the third year (p<0.01).
Table 3 demonstrates the change in visual acuity throughout the study period of three years in the different groups.

DISCUSSION

AMD is a progressive disease in nature, and the visual acuity of nAMD patients tends to decline over the years. Rate of deterioration varies between patients and is associated with multiple risk factors, including genetic, phenotypic, demographic, and environmental factors.(18) Although intravitreal anti-VEGF injections have revolutionized the management and treatment options for nAMD patients,(19) the natural deterioration in VA remains a challenge. Different studies have previously demonstrated the decline in patients' vision despite treatment, and an example for that would be found in the MARINA and ANCHOR studies, in which nAMD patients received monthly intravitreal injections of Ranibizumab, and as a result their vision improved at the first year of follow-up, with a mean gain of 7.2 and 11.3 letters respectively. (20,21) In both studies, although patients had still better vision compared to their baseline, their visual acuity started a trend towards declining, and after 24 months their mean gain was 6.6 and 8.1-10.7 in the MARINA and ANCHOR studies, respectively. (20,22) By the end of the fourth year, as was demonstrated by the HORIZON study, the patients' vision averaged with only 2.0 letters better than their baseline VA,(23) and furthermore, in the SEVEN-UP study, which evaluated the patients from the ANCHOR and MARINA studies for a total time of seven years from initiation, the trend in VA continued, as it was found that the mean visual acuity further declined, down to -8.6 letters from baseline after seven years.(24)

In this current study, baseline VA were similar between the three groups and differed significantly by the end of the third year (final VA) with VA of 0.50±0.41 for the no-delta group, compared with the 0.59±0.46 and 0.61±0.50 in the mid and high delta injection index groups, respectively ($p=0.035$). in addition, the mid and high delta injection index suffered statistically significant decline in VA, while the no-delta injection index group patients experienced a non-statistically significant and lower decline in their VA. The above-mentioned difference suggests that the natural progression of the disease was not the main factor differentiating between the patients from the three groups, as it is reasonable to assume statistical similarity between the groups.

Number of injections:

Real world data suggests that patients tend to receive less frequent injections than needed over the years.(24) Possible explanations include the high burden of injections causing poor compliance and loss of functional vision due to the natural course of the disease secondary to fibrosis and atrophy.(10,11) Several studies have showed that more frequent injections and follow-up may lead to better visual outcomes.(14,15) The CATT research group compared between Ranibizumab and Bevacizumab in PRN versus monthly regimens in previously untreated patients. They showed that during a study period of one year, the gain in VA was slightly better with monthly regimen compared with PRN regimen, although not statistically significant. The patients in the Ranibizumab monthly group gained +8.8 letters, as compared with the +6.7 letters in the PRN group. Similar results were obtained for the Bevacizumab monthly (+7.8 letters) versus PRN (+5.0 letters).(13) Likewise, the HARBOR and IVAN trials had similar results with a little advantage to monthly injections over PRN protocols.(14,15)

The main goal of this study was to investigate the effect of the delta in the number of yearly injections on VA of neovascular AMD patients, as increased injection index was previously reported to be associated with better mean visual acuity in patients with pigment epithelial detachment secondary to AMD. Over the course of 5 years, a gain of approximately 0.5 EDTRS letters was reported for each additional annual injection.(17) The study population included patients who have already been treated with intravitreal anti-VEGF injections for a year before the beginning of the follow up period, as patients' vision tends to improve at the first year of treatment and the deterioration is prominent in the following years, as was previously reported.(20,21) In this current study, all patients received a similar number of injections in the first year of follow up and were then divided into three groups based on the delta in the number of injections in the second and the third years of study. Indeed, the number of annual injections was significantly different between the three groups after 3 years with 6.8±2.5 in the no-delta group, and 5.5±2.5 and 4.1±2.7 in the mid and high delta injection index groups, respectively ($p<0.01$).

Our main finding was that high delta injections index is associated with less favorable visual outcomes. This finding is consistent with reports from previous studies. For example, a subgroup of patients in the SEVEN-UP trial has demonstrated that patients who received more injections were more likely to gain vision, with +3.9 letters for the >11 injections group, in comparison with their counterparts who received 6-10 injections, and had a mean loss of 10.8 letters.(24) Moreover, a study by Oubraham et al. compared the VA gained by nAMD patients treated in PRN versus Treat-and-Extend regimens over a 12-month period. They attributed the better vision achieved by the T&E group to the significantly larger number of injections given to this group compared to the PRN group.(25) An additional study by Spaide also suggested a dose-response relationship between the number of injections and the response to treatment.(26) Our study demonstrates for the first time that not only the total number of injections has an impact on visual acuity of nAMD patients, but also the relative change in the number of injections.

LIMITATIONS

Limitations of this study including its retrospective nature and lack of OCT findings. Therefore, we were unable to investigate the considerations of retina specialists for planned intervals between injections for each patient, nor to study the causes of why patients may have missed their scheduled follow-up appointments, which caused them to skip planned injections.

CONCLUSIONS

In this study we found an association between worse visual acuity and lower rate of injections per year, as with every decrease of injections from baseline, patients vision deteriorated accordingly. This finding highlights the importance of continuous follow-up and good adherence of patients to the prescribed treatment, as it has a significant implication on their visual acuity.

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COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

AUTHORS CONTRIBUTIONS

All authors have made substantial contribution to the study conception and design, and the analysis and interpretation of the data. Material preparation, data collection and formal analysis were performed by Reut Shor MD, Ori Segal MD, Eran Greenbaum MD, Omer Trivizki MD, and Shai Cohen MD. The first draft of the manuscript was written by Ram Cohen and was reviewed and edited by Gilad Rabina MD with the supervision of Anat Lowenstein MD.

All authors revised the previous versions of the manuscript. All authors read and approved the final manuscript.

All authors included on this paper fulfil the criteria of authorship, and declare that there is no one else who fulfils the criteria that has been excluded as an author.

ETHICS APPROVAL

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 Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, approval number [TLV-1039-20]. The research adhered to the tenets of the Declaration of Helsinki.

CONSENT TO PARTICIPATE – Not applicable

CONSENT TO PUBLISH - Not applicable

DATA AVAILABILITY

All data generated or analyzed during this study are included in this article or its supplementary material files. Further enquiries can be directed to the corresponding author.

Ram Cohen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1 Demographics and Baseline Characteristics

	No-delta injection index (N=226)	Mid-delta injection index (N=475)	High-delta injection index (N=443)	P-Value
Gender (FEMALE)	57.9%	57.6%	57.5%	0.995
Age	81.8±8.6	80.8±8.9	80.4±9.0	0.176
Baseline VA	0.37±0.31	0.39±0.31	0.41±0.34	0.115
Final VA	0.50±0.41	0.59±0.46	0.61±0.50	0.035
Number of Injections	20.4±7.1	18.7±5.8	15.9±5.2	<0.01

Table 2 Mean number of injections per year in no-delta, mid-delta, and high delta injection groups

	1st Year Injections	2nd Year Injections	3rd Year Injections
No-delta (N=226)	6.8±2.3	6.8±2.4	6.8±2.5
Mid-delta (N=475)	7.1±2.0	6.1±2.2	5.5±2.5
High delta (N=443)	6.9±2.5	4.9±3.2	4.1±2.7
P- Value	0.345	<0.01	<0.01

Table 3 Change in VA over the years in no-delta, mid-delta and high delta injection index groups

	Baseline VA	1 Year VA	2 Year VA	3 Year VA	P-Value
No-delta injection index (N=226)	0.37±0.31	0.42±0.36	0.46±0.37	0.50±0.41	0.051
Mid-delta injection index (N=475)	0.39±0.31	0.49±0.40	0.54±0.43	0.59±0.46	<0.01
High delta injection index (N=443)	0.41±0.34	0.48±0.41	0.54±0.47	0.61±0.50	<0.01

Fig.1 The change in VA for the no-delta, mid-delta, and high delta injection index groups.

