Neovascular Age-Related Macular Degeneration (Narmd), Monitoring the Effectiveness of a Stable Treatment: A Prospective Study

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Abstract

This study aims to demonstrate the effectiveness of a stable treatment, with relevant and long-term results, in patients diagnosed with neovascular AMD. The data were collected by analyzing the best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) images at the first visit and the last visit after two years of follow-up. This study compares the functional and structural visual results between patients who did not regularly follow their planned intravitreal anti-VEGF injection intervals with those who did. Currently, there are no studies in our country that certify the correct management of treatment for nAMD patients or optimal eye care services to support them. This is important for creating evidence and strategies for better treatment and monitoring of patients with advanced neovascular AMD. This study identifies the role of correctly adhering to treatment for maintaining optimal BCVA and the quality of life of people at risk of progression to late AMD. The group of patients with nAMD who did not adhere correctly to the planned intravitreal anti-VEGF injections had worse functional and structural results in BCVA and OCT. We recommend emphasizing the importance of maintaining continuity of care for neovascular AMD patients to achieve better results in BCVA and quality of life.

Keywords: *wet AMD, BCVA, intravitreal anti-VEGF, PED, OCT*

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of low vision and loss of central vision in patients over the age of 45 years in united states populations (Ayoub, 2009) even in Albania visual impairment had an influence in quality of life (Marsida Krasniqi & Trebicka, 2020). Advanced AMD has higher prevalence in european population over 60 years old than early AMD , while the incidence of any late AMD in Europe is estimated to increase with 15% by 30 years (Wang et al., 2022). Even though the most frequent form is dry AMD, there is still no definitive therapy and the central vision is seriosly compromised because of the chronic irreversible damage of RPE, neuroretina and choriocapillaris (Rickman, Farsiu, Toth, & Klingeborn, 2013). Based on exudative process AMD has the dry form whith no exudates and the wet form or exudative form. The exudative form is characterized whith macular neovascularization, pigment epithelial detachment, which are the main causes of rapid and important vision loss. The dry form and wet form of AMD are 90%

and 10% respectively (Mardani, Jahromi, Naieni, & Zeinali, 2003), (Song, Liu, Shang, & Ma, 2022). Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are the most efective and used treatment for macular edema and neovascularization in wet AMD patients (Hang, Feldman, Amin, Ochoa, & Park, 2023). Other studies have used corticosteroid for macualr edema (M Krasniqi & Nallbani, 2022), (Antonio, Guimaraes, Varela, Georgiou, & Michaelides, 2020). In manner to control the chonic damage and maintain a stable visual acuity, there are two types of anti VEGF regimen;"observe and plan" (Lanzetta, Loewenstein, Vision, & Steering, 2017), (Marsida Krasniqi & Nallbani, 2021), in which anti VEGF injection are planned to be performed repeatedly in very careful studied intervals or ''treat and extend'' regimen in which the periodically adjusted distance of aplication of anti VEGF according to disease activity. The desease activity is based on visual acuity measured by BCVA (best corrected visual acuity) and anatomical parameters obtained from optical coherence tomography (OCT). During pandemic from COVID-19 were abruptly cancelled medical apointment ad planned interventions all medical fields (Id et al., 2023), including ophthalmology (Sen, Honavar, Sharma, & Sachdev, 2021). Other infection disease have been a challenge for public health (Marsida Krasniqi & Bino, 2016). The evidences showed incerased number of patient which afraid of getingthe COVID 19 avoided to present to scheduled intravitreal anti-VEGF injection visits for the treatment of their nAMD (Nassisi et al., 2023). Studies have confermed increased evidence of permanent vision loss if not treated regularly with intravitreal injections, so this complicate the wet AMD treatement (Lam et al., 2021). AAO suggested that the treatment with anti VEGF is considered an urgent and emergent care and the treatment modality should be mantained (Ayoub, 2009), (Hadziahmetovic, Malek, & Martin, 2021). Still till 2024, some patients refused or were unable to visit, which led many patients to refrain from their routine intravitreal anti-VEGF injection appointments, allowing us to evaluate the role of designated intervals in the treatment of patients with wet AMD, in Albania even the economic part is a problem for ministry of health (Trebicka, Harizi, Krasniqi, Kalaja, & Tartaraj, 2024). Studies about AMD in Albania are not much, but they found effect in improvement in visual acuity in patients treated with anti VEGF (Mema et al., 2022).

This study aimed to compare the results in functional and structural retina and visual outcomes between patient with nAMD who did not follow the treatement with intravitreal anti-VEGF injection in planned intervals (group 1) with those who did (group 2).

2. Materials and Methods

This study utilized data from patients diagnosed with neovascular age-related macular degeneration (nAMD) treated at the University Trauma Hospital and Mother Teresa University Hospital in Tirana. We analyzed best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) data collected during each patient's initial and final visits across a two-year timeframe. The "first visit" was defined as the patient's last appointment in early June 2022, where BCVA and OCT measurements were initially taken. The "last visit" referred to each patient's first appointment in June 2024, with both assessments completed.

Patients included in the study were diagnosed with any type of nAMD (Types I, II, or III) and received intravitreal anti-VEGF injections from June 2022 to June 2024. Patients with other retinal pathologies, such as CRVO, BRVO, or high myopia, or those without complete BCVA or OCT data before or after the designated period, were excluded. BCVA results were reported using Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores.

Participants were divided into the following groups:

- **Group 1 (non-adherence):** Patients who missed at least one scheduled anti-VEGF injection during the study period.
- **Group 2 (adherence):** Patients who completed all scheduled anti-VEGF injections during the study.

The main study outcomes were BCVA and OCT results. BCVA outcomes were categorized as follows:

- **Positive BCVA outcome:** A loss of fewer than five ETDRS letters from the first to the last visit, stable BCVA, or an increase in BCVA.
- **Negative BCVA outcome:** A loss of five or more ETDRS letters from the first to the last visit.

OCT biomarkers evaluated for disease progression included:

- Changes in intraretinal fluid (IRF),
- Changes in subretinal fluid (SRF), and
- Presence of pigment epithelial detachment (PED)

These factors were assessed one by one by the operator. A negative IRF outcome was defined as IRF present on the OCT scan at the last visit but absent at the first visit; stable or reduced IRF was considered a positive outcome. SRF and PED were evaluated in a similar manner. The OCT result was considered negative if there was an increase in any of

the IRF, SRF, or PED markers, and positive if there were no such increases.

2.1 Injection Interval

The real injection interval was the actual interval patients followed during the study, while the assigned injection interval was the target interval recommended for each patient by June 2024.

2.2 Data Sources and Statistical Analysis

The data collected were stored in an Excel database and analyzed in coded and anonymous form. Using SAS software at a significance level of $\alpha = 0.05$, we performed the statistical analyze. Means with standard deviations (±SD) and frequencies (percentages) were calculated. The paired t-test was used to compare numeric variables between the first and last visits, while Fisher's exact test and the Mann-Whitney U test were applied to categorical and continuous variables between groups. A power analysis determined a sample size of approximately 180 participants to detect a 20% difference with an 80% power at the 5% significance level. Multivariate logistic regression with stepwise variable selection (thresholds of $P \leq 0.25$ to enter and $P \geq 0.10$ to exit) was used to identify independent predictors of negative BCVA outcomes.

3. Results

3.1 Patient Demographics and Group Characteristics

The study analyzed 33 patients, divided into Group 1 (non-adherent) and Group 2 (adherent). No significant gender differences were found between the groups. However, females were predominant in both.

Gender	Group 1 (n = 15, 47 eyes)	Group 2 (n = 18, 29 eyes)	P-value
Female, n (%)	10 (66.67%)	13 (72.23%)	0.43
Male, n (%)	5 (33.33%)	5 (27.77%)	

While both groups had more female participants, no significant differences in gender distribution were observed (P = 0.43).

3.2 Age Comparison

Group	Mean Age (years) ± SD	P-value
Group 1	75.16 ± 6.34	0.34
Group 2	73.12 ± 6.58	

Age differences between groups were not statistically significant.

3.3 Injection Interval Analysis

The assigned injection intervals differed significantly between the groups, with Group 2 (adherent) receiving injections more frequently, whereas Group 1 (non-adherent) had longer real injection intervals.

Injection Interval	Group 1 Mean ± SD (months)	Group 2 Mean ± SD (months)	P-value
Assigned	1.28 ± 0.46	1.75 ± 0.70	< 0.0001
Real	2.76 ± 0.96	1.77 ± 0.70	< 0.0001

Group 1's real injection intervals exceeded their assigned intervals, indicating deviation from the planned schedule. Group 2 adhered more closely, receiving injections at shorter intervals.

3.4 Best Corrected Visual Acuity (BCVA) Outcomes

At the first visit, BCVA scores were similar between groups. However, by the study's conclusion, Group 1 experienced a higher rate of negative BCVA outcomes than Group 2.

BCVA Outcomes	Group 1	Group 2	P-value
Initial BCVA (ETDRS letters)	66.65 ± 18.04	65.66 ± 19.03	0.68
Negative BCVA Outcomes (%)	41.3	27.9	0.04

Although initial BCVA scores were comparable, Group 1 had a significantly higher proportion of negative outcomes, suggesting that adherence to injection intervals may impact BCVA.

3.5 Optical Coherence Tomography (OCT) Outcomes

Group 1 showed a higher rate of negative OCT outcomes, with notable factors including increased intraretinal fluid (IRF) and pigment epithelial detachment (PED).

OCT Outcomes	Group 1 (%)	Group 2 (%)	P-value
Negative OCT Outcomes	51.4	13.1	< 0.0001
IRF	79.16	87.5	0.047
PED	83.33	93.75	0.0038

Group 1 had a significantly higher proportion of unfavorable OCT outcomes. Elevated IRF and PED levels in Group 1 may contribute to poorer outcomes.

3.6 BCVA Change Over Time by Outcome Type

Group 1's BCVA changes were less favorable than Group 2's, with greater BCVA loss in patients with unfavorable outcomes.

BCVA Change (ETDRS letters)	Group 1 Mean ± SD	Group 2 Mean ± SD	Range
Favorable Outcomes	5.00 ± 8.40	4.41 ± 8.16	[0, 40]
Unfavorable Outcomes	-7.78 ± 5.28	-8.82 ± 4.27	[-30, -5]

Patients in Group 1 with unfavorable outcomes had slightly less BCVA loss than those in Group 2. However, Group 2 showed overall more stable outcomes with a narrower range of change.

3.7 Predictive Analysis of Unfavorable BCVA Outcomes

Using multivariate analysis, extended real injection intervals and higher BCVA at the last pre-study visit were independently associated with negative BCVA outcomes.

Predictive Factors for BCVA	Effect on Outcome	P-value
Real Injection Interval	Positive correlation	0.03
Last Visit BCVA	Positive correlation	0.02
OCT Outcome	No correlation	

Maintaining the assigned injection interval appears critical to reducing the likelihood of negative BCVA outcomes.

4. Discussion and Conclusions

The objective of this study was to demonstrate the long-term effectiveness of treatments and the most relevant retinal changes in OCT in patients affected by neovascular AMD. We divided the neovascular AMD patients considering their adherence to antiVegf therapy, into two groups: Group 1 were patients who did not follow correctly their planned anti-

VEGF injection intervals, while Group 2 included those who did. Results between the two groups were compared. The functional outcomes assessed were based on best-corrected visual acuity (BCVA). The anatomical functional outcomes were based on OCT imaging of the retina.

Our study demonstrated that Group 1 compared to patients in Group 2 had significantly more negative BCVA outcomes (by 13.41%, P = 0.04) and worse OCT biomarkers (P < 0.001). Regression analysis showed that longer injection intervals, in patient with a lower BCVA at the first visit, in the last visit the results in BCVA were very compromised. Indeed, the most affected groups were groups with better visual acuity and patients who delayed their injection visits.

Similar results to this was the study by Borrelli et al. during the COVID-19 pandemic in Italy, where BCVA and OCT results during the quarantine period were significantly worse for patients with wet AMD compared to their visits before pandemic in time which they followed regularly their planned treatment (Borrelli et al., 2020) . An important result of our study is the association between negative BCVA outcomes and extended intervals in patients who delayed their injections, a finding that was also demonstrated by Borrelli et al. in their pandemic study (Borrelli et al., 2020). Our study, along with those of Borrelli et al. showed that maintaining stable and relatively satisfying vision is dependent on following the planned intervals of visits and anti-VEGF injections. Naravane et al. (Borrelli et al., 2020) also conducted a similar study at a retina center in the USA, where they reported that patients who did not aply in time their planned intravitreal injection with antiVEGF had significantly negative BCVA outcome compared to those who adhered to the scheduled therapy.

The most relevant OCT changes in neovascular AMD patients were seen in the fluid location in the retina, so if was intra or subretina or pigment epithelial detachement (IRF,SRF or PED) and type of fluid(cystic,edematous, sierous or hemorragic) (Borrelli et al., 2020). These parameters are considered important OCT biomarkers, as studies conducted by Wickremasinghe et al and Schmidt-Erfurth et al. have shown that best corrected visus was better in eyes without presence of IRF/SRF (cysts or edema) than in eyes with present and persistent IRF/SRF (Macular et al., n.d.) . Other studies demonstrated the impact of PED in having worst vision outcome after individualized anti-VEGF therapy in patients with AMD (Macular et al., n.d.), (Xiong et al., 2020).

In our study, when we compared the elevation rate in PED and IRF during the first visit, Group 1 showed a significantly higher rate of unfavorable OCT outcomes (P = 0.0003) than Group 2 (P = 0.047), with a significant p-value for Group 1. We compared our results with the findings of Schmidt-Erfurth and Waldstein and were at the same outcome in supporting the importance of injecting intravitreal anti-VEGF continuosly (Lanzetta et al., 2017). The data were analyzed statistically to identify an association between unfavorable outcomes in BCVA and OCT , but did not find any significant correlation. Others studies have shown that not only anti-Vegf have influence in a positive improvement of BCVA, but even other treatment as corticosteroids (M Krasniqi & Nallbani, 2022). This results may have been influenced by other factors we did not consider, because the patient follow-up period was limited in two year period (2022-2024), with data on first and last visit not long enough for a multivariate logistic regression analysis. Our study was designed in a retrospective use of data from patients who met the selection criteria recorded in limited period of time as required by the study. This short follow-up time was a limitation. In this study similar to Tsiroupolous et.al we could not understand long-term effects in patients who did not respect their intervals of intravitreal injection of anti VEGF (Marsida Krasniqi & Nallbani, 2021), (Lam et al., 2021). In the future we need to perform studies with a bigger number of patients with a larger period of follow-up in time, so the study bias and and impact of thie study can be more efficient. The study was also subject to several limitations, including the risk of selection and recall bias, and the potential confounding results. As a conseguent bias, our multivariate logistic regression analysis has chances that we could not identify factors that can predict an unfavourable BCVA outcome. Furthermore, our study can be used as support to future home-monitoring OCT devices to help identify threatening biomarker changing in patients with neovascularAMD whose visual function may go worse in the near future (Song et al., 2022). This study will help fitting better therapy aderence and outcome from the follow up. Telemedicine tools and new AI technologies based in this studyes could also be useful in decreasing the number of visit per patient, creating a remote monitoring of the desease.

The treatment interruptions experienced by a significant number of patients due to loss of follow-up allowed us to confirm the importance of being persistent in the treatment and follow-up of nAMD patients. Maintaining strict adherence to the treatment plan leads to better structural retinal profiles on OCT, which can translate into improved visual acuity and a better quality of life.

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