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Clinical characteristics and intravitreal aflibercept outcomes in patients aged 90 years and older with neovascular age-related macular degeneration

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Abstract

Background Age-related macular degeneration (AMD) stands as the primary cause of visual impairment and blindness among the elderly population. Patients over 90 years comprise a unique demographic that may necessitate particular attention. The aim of this study was to examine the clinical characteristics and treatment outcomes in patients aged 90 years or older diagnosed with neovascular age-related macular degeneration (nAMD).

Methods The medical records of treatment-naive patients aged ≥ 90 years diagnosed with nAMD have been retrospectively reviewed in our clinic. The complete ophthalmic examination findings of the patients, along with optical coherence tomography and fundus fluorescein angiography records, as well as their adherence to treatment, and reasons for treatment discontinuation were noted. Clinical data following intravitreal injection loading dose and during the 1st and 2nd years of treatment were evaluated.

Results The average age of the 45 participants (25 females, 20 males) included in the study was 93.55 ± 5.2 years (range; 90–101). The mean best-corrected visual acuity at diagnosis, at the 4th month of treatment, and during the 1st and 2nd years were LogMAR 0.8, 0.5, 0.7 and 1.0, respectively. The most common reasons for missing appointments and completely discontinuing treatment were death and inability to attend appointments due to additional comorbidities.

Conclusion In the very elderly patient group, nAMD can lead to severe damage in the macula, and a decrease in visual acuity despite treatment is not uncommon. Close monitoring and support for treatment adherence are necessary for this group of patients.

Keywords Age related macular degeneration, Elderly, Geriatrics, Vision loss

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Introduction

In the coming decades, the proportion of the older persons within the total population will continue to increase. Particularly in old age, preserving visual function is crucial to prevent falls and consequent injuries requiring treatment, resulting in permanent disabilities and potential need for care [1]. Neovascular age-related macular degeneration (nAMD) greatly impairs central vision, leading to difficulties in daily activities such as communicating, navigating, reading and recognizing faces, which is particularly burdensome for individuals over 90 [2]. This loss of independence and increased reliance on others can contribute to feelings of frustration, anxiety, and depression, highlighting the significant impact of nAMD on the overall quality of life in this age group.

AMD is a leading cause of blindness among adults in developed countries. The overall incidence of AMD increases significantly with age. The yearly occurrence of AMD varies, with rates ranging from 0.3 per 1000 individuals among those aged 55 to 59 years to 36.7 per 1000 individuals among those aged 90 years or older [3]. AMD manifests in two primary forms: dry or neovascular AMD. nAMD which represents a late stage of the disease, is less common but more severe than dry AMD, accounting for about 10–15% of cases [4]. nAMD is characterized by the growth of abnormal blood vessels beneath the retina, a process known as choroidal neovascularization. Anti-vascular endothelial growth factor (anti-VEGF) injections are the primary treatment for nAMD, aimed at suppressing the growth of abnormal blood vessels and preserving vision. Aflibercept which is one of the commonly used anti-VEGF agents was approved following the publication of the results of the VIEW 1 and 2 studies [5]. The treatment regimens are intensive with monthly intravitreal injections for 3 months, followed by varying re-treatment regimens depending on the clinical course. The introduction of anti-VEGF treatment has made it possible to improve or at least stabilize visual acuity and visual function in the majority of patients.

The natural biological process of aging significantly impacts the body, including the macula, which undergoes a range of changes. With aging, the number of retinal pigment epithelium (RPE) cells decreases disproportionately to photoreceptors, and metabolic and oxidative stress increases in RPE cells [6]. Consequently, these vulnerable cells become relatively resistant to anti-VEGF therapy.

Despite advancements in ophthalmic care, understanding the clinical characteristics and treatment outcomes of nAMD in individuals over 90 years old is essential to improving management strategies and patient care. While numerous high-quality epidemiological studies on AMD have been conducted, the representation of patients aged 90 and older remains limited. This underrepresentation can be attributed to several factors, including physical or cognitive limitations, transportation challenges, reluctance to attend frequent follow-ups, high mortality rates, and the risk of confounding factors. Therefore, this study aimed to explore the clinical features and treatment responses of treatment-naive patients aged 90 years and above diagnosed with nAMD, elucidating the challenges and considerations specific to this vulnerable population.

Methods

The medical records of treatment-naive patients with nAMD who presented to our clinic between 2013 and 2017 were included in this retrospective chart review. All subjects were informed about the disease and treatment protocols, and informed consent for intravitreal injections was obtained. This study followed the tenets of the Declaration of Helsinki and the protocol was approved by the local Ethics Committee.

All patients underwent optical coherence tomography (OCT) and fluorescein angiography to confirm the diagnosis of nAMD at baseline visit. The exclusion criteria were as follows: patients with other retinal vascular diseases, those who had undergone previous retinal surgery or laser procedures, individuals with any macular disease other than AMD, and those who had been previously treated with anti-VEGF therapy. If a patient has bilateral nAMD, we utilize only one eye to avoid statistical issues. The best-corrected visual acuity (BCVA) values were obtained through Snellen examination and subsequently converted to LogMAR equivalents. Biomicroscopic examination, dilated fundus examination, and swept-source optical coherence tomography (OCT) (DRI-OCT-1, Topcon, Tokyo, Japan) were performed, and the results were recorded at each visit. According to the VIEW protocol, which consists of 3-monthly intravitreal aflibercept injections during the loading phase, followed by repeated bimonthly injections thereafter throughout the entire first year of treatment, a "Treat and Extend" protocol was applied between first and second years of the study. Follow-ups were conducted at baseline, the 4th month after the loading dose and at the first and second years.

The reinjection criteria included a visual acuity decline exceeding 5 letters (Snellen equivalent to 1 line), an increase in central macular thickness (CMT) of ≥ 100 µm, the presence of intraretinal and/or subretinal fluid, the observation of leakage on fluorescein angiography, and new macular or subretinal hemorrhage.

Data analysis was performed by using SPSS for Windows, version 23 (IBM Corp., Armonk, NY, USA). Descriptive statistics were shown as mean $\pm$ standard deviation (SD) or percentages. The mean visual acuity and CMT values were compared using repeated measures ANOVA with post-hoc Bonferroni correction. A

p value less than 0.05 was considered statistically significant. An a priori power analysis was conducted using G*Power version 3.1.9.7 to determine the minimum sample size required to test the study hypothesis. The results indicated that a sample size of $N=45$ would be required to achieve 80% power for detecting a medium effect, with a significance criterion of $\alpha=0.05$, for a one-sample t-test.

Results

A total of 45 eyes from 45 patients, aged between 90 and 101, who received intravitreal aflibercept for nAMD, were included in this study. The demographics and characteristics of the patients are shown in Table 1.

Change in visual acuity

The mean BCVA at diagnosis, at the 4th month of treatment, and during the 1st and 2nd years were LogMAR 0.8, 0.5, 0.7 and 1.0, respectively. The pairwise comparisons indicate significant changes in visual acuity across the four study time points. Between baseline and 4th month, there was a significant improvement in VA, with a mean difference of -0.167 ($p<0.05$). Similarly, VA improved significantly between 4th month visit and 1st year (mean difference=0.118, $p<0.05$). However, there was no significant change between baseline and 2nd year visit, as the mean difference was small and non-significant (0.007, $p=1.0$). While the difference between 1st year and 2nd year was marginally non-significant (mean difference=0.057, $p=0.053$), it suggests a trend towards stabilization of VA after 1st year. These results suggest that the most notable improvements in VA occurred between the earlier time points, with stabilization observed towards the later stages of the study.

Change in CMT

The mean CMT (SD) at baseline, at the 4th month of treatment, and during the 1st and 2nd years was 443 (156), 325 (123), 349 (119), and 352 (117) μm, respectively. The analysis of central macular thickness (CMT) at four study time points showed significant changes over time. Specifically, CMT decreased significantly from the baseline visit compared to the 4th month, first, and second year, with mean differences of 114.61 μm, 95.56 μm, and 94.15 μm, respectively, all reaching statistical significance ($p<0.05$). However, no significant differences were observed between 4th month, 1st year, and 2nd year, indicating that most of the reduction in CMT occurred between the baseline and subsequent visits, with stabilization thereafter.

During the two-year study period, a total of nine patients passed away. Reasons for discontinuation of treatment included primarily the burden of treatment (seven patients), largely attributable to systemic comorbidities, referral to another center (five patients), and cessation of injections due to the development of fibrotic dry scar (five patients).

Discussion

In this study, we assessed the clinical characteristics and treatment outcomes of nAMD in a specific group of patients aged 90 years or older. Our findings suggest that intravitreal aflibercept is effective, particularly during the first months of treatment in this very elderly population with nAMD. Furthermore, we observed a high rate of treatment discontinuation or missed appointments due to mortality or other comorbidities within this patient cohort.

In recent years, due to the increased life expectancy worldwide, the number of patients affected by nAMD is

Table 1 Demographics and clinical characteristics of the patients with neovascular age-related macular degeneration aged ≥ 90 years

	***N*=45**			
Age at diagnosis (years), mean ± SD	93.55 ± 5.2			
Gender (N), female/male	25/20			
Lesion type (N)				
Predominantly classic	18			
Predominantly occult	27			
	Baseline (1)	*4th month (2)*	*1st year (3)*	*2nd year (4)*
BCVA (Snellen decimal)	0.16	0.32	0.2	0.1
BCVA (LogMAR)	0.8	0.5	0.7	1.0
P value**	(1–2) $p<0.001$* (1–3) $p<0.001$* (1–4) $p=1.0$ (2–3) $p<0.001$* (2–4) $p<0.001$* (3–4) $p=0.053$			
Mean CMT (μm) (SD)	443 (156)	325 (123)	349 (119)	352 (117)
P value**	(1–2) $p=0.001$* (1–3) $p=0.009$* (1–4) $p=0.01$* (2–3) $p=1.0$ (2–4) $p=1.0$ (3–4) $p=0.9$			

BCVA: Best corrected visual acuity, CMT: Central macular thickness, SD: Standard deviation, *Statistically significant **P value was calculated by ANOVA test

One eye of the patients included in the study was treatment-naive for nAMD, while all patients had a macular issue in the other eye as well: dry AMD in 15 patients (33%), geographic atrophy in 11 patients (24%), old macular scar due to AMD in 10 patients (22%), nAMD requiring treatment in 9 patients (20%). The mean number of aflibercept injections administered over a two-year period was 11.77 ± 1.51

gradually rising. In a study, it was observed that approximately 40,000 new cases were added annually, and the oldest people constituted 8% of the new cases presented [7]. When natural age-related macular changes, such as loss of RPE cells, inadequate management of reactive oxygen species, and diminished debris and nutrient exchange due to thickening of Bruch's membrane, coincide with genetic and pathogenetic factors, they collectively contribute to the progression of AMD disease [8]. In individuals aged 90 years and above, the genetic variant rs6565597 exhibited specific effects, while a protective variant showed a minor effect. Thus, these genetic factors may contribute to the pathogenesis of AMD within this age group [9].

In a histological study of subjects over 90 years old, age-related macular changes that are not clinically detectable as macular degeneration include the accumulation of lipofuscin granules in the retinal pigment epithelium, loss of foveal photoreceptors, degeneration of pigment epithelial cells, thickening of Bruch's membrane due to heterogeneous debris, and a reduction in the choriocapillaris [6]. Therefore, patients aged 90 and above represent a distinct and particularly vulnerable subgroup within the AMD population, requiring a separate evaluation of their characteristics to enhance late-stage AMD risk assessment and patient care. In the current study we found that the mean BCVA at diagnosis, at the 4th month of treatment, and during the 1st and 2nd years were LogMAR 0.8, 0.5, 0.7 and 1.0, respectively. The combined analysis of VIEW 1 and VIEW 2 studies revealed an average gain of 8.4 letters in visual acuity at year 1; however, data concerning the specific efficacy changes in very elderly subgroup undergoing treatment for AMD remains limited [5]. *Subhi et al.* noted that mean change in BCVA was 3.2, 1.5, and −2.2 ETDRS letters at 4, 12, and 24 months, respectively, and found Aflibercept to demonstrate superior visual and anatomical outcomes compared to Ranibizumab [2]. *Chatziralli et al.* compared aflibercept outcomes in nAMD patients aged 90 years or older with those younger than 90. They reported that, in patients under 90 years old, the average improvement in visual acuity was +4.6 letters at year 1 and +2.1 letters at year 2. Conversely, patients aged 90 years or older experienced an average increase of +3.1 letters in visual acuity at year 1, but a decrease of 0.8 letters at year 2 [7]. They noted that the decreased visual acuity in the older group may indicate a higher prevalence of concurrent atrophic changes compared to the younger group. Additionally, they showed that very old patients with nAMD benefited from aflibercept therapy in some degree, but these benefits were not as pronounced as those observed in younger patients. While anti-VEGF injections are effective in improving both visual acuity and anatomical outcomes during the early stages of treatment, the progressive nature of AMD, the development of fibrosis or atrophy, and possible reduced responsiveness to therapy, combined with high non-adherence rates in the very elderly age group, contribute to a decline in visual outcomes by the end of the second year. Similarly, in our study, the most notable improvements in visual acuity occurred between the earlier time points, with stabilization observed towards the later stages of the study. Age-related changes in retinal structure and function, increased oxidative stress, systemic factors, metabolic activity decline, and immune senescence may collectively contribute to the reduced response to anti-VEGF injections in individuals over 90 years old with nAMD [10].

The treatment of nAMD necessitates frequent intravitreal injections, posing challenges for treatment adherence among patients, particularly the elderly, and increasing the healthcare burden for their caregivers. The number of systemic comorbidities, inadequate caretaker assistance, and lower baseline vision were noted as primary factors contributing to non-adherence and non-persistence in AMD treatment. The highest risk was observed in individuals over 90 years old, with a threefold higher risk compared to those under 80 years of age [11]. A recent systematic review on the factors influencing non-adherence to intravitreal injections demonstrated that advanced age and associated comorbidities significantly impact adherence to and persistence with therapy [12]. In our study, a significant proportion of our patients ceased treatment either due to mortality, or the unacceptable burden associated with the treatment regimen, exacerbated by additional illnesses. Similarly *Subhi et al.* observed that during the 2-year follow-up, 59 patients (51%) discontinued treatment, underscoring the specific challenges associated with managing patients aged 90 years or older [2]. Mortality was a concern during the follow-up period. During our study period, 9 out of 45 patients passed away. Similarly, in the study by *Subhi et al.* [2], it was observed that 16 of the 59 patients who discontinued treatment had died. In a systematic review, worse baseline visual acuity and poor response to treatment have been reported to be associated with a higher risk of both non-adherence and non-persistence in intravitreal injection therapy [11]. In another study, patients that discontinued treatment tended to be older, with a higher proportion falling within the over 90 age group, and exhibited poorer baseline vision [13]. Contrary, *Chatziralli et al.* concluded that, in their study, the discontinuation rate was deemed acceptable, and the very elderly patients demonstrated adherence to the intensive anti-VEGF treatment regimens.

The main limitation of our study was its retrospective nature. Additionally, the study population was relatively small and we did not have a control group. Prospective population based studies with a large sample size can

better evaluate the clinical characteristics and treatment outcomes of nAMD in elderly adults over 90 years of age.

In conclusion, intravitreal aflibercept is effective particularly during the first months of treatment in patients over 90 years old with nAMD. In the very elderly patient group, who already have a vulnerable macula, nAMD can cause significant damage to the macula, and a decrease in visual acuity despite treatment is not uncommon. This patient cohort has a high rate of treatment discontinuation or missed appointments due to mortality and other comorbidities. Therefore, it is imperative for healthcare providers and caregivers to offer comprehensive support and assistance to help these individuals navigate the challenges associated with this condition, thereby promoting their independence and overall well-being for as long as possible.

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Author contributions
FU constructed the main idea and hypothesis of the study, collected the data, wrote, reviewed, and approved the final version.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All subjects were informed about the disease and treatment protocols, and informed consent for intravitreal injections was obtained. This study followed the tenets of the Declaration of Helsinki and the protocol was approved by the Recep Tayyip Erdogan University Ethics Committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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