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Real-life neovascular AMD treatment considering reimbursement in Turkiye: One-year comparison of switching to intravitreal ranibizumab or aflibercept after treatment failure with three loading intravitreal bevacizumab injections

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ABSTRACT

OBJECTIVE: To compare one-year anatomical and functional results of switching to an on-label intravitreal anti-vascular endothelial growth factor (anti-VEGF) agent (intravitreal ranibizumab [IVR] or aflibercept [IVA]) after treatment failure with three loading doses of off-label intravitreal bevacizumab (IVB), which is mandatory in the treatment of neovascular age-related macular degeneration (nAMD) to get reimbursement from Social Security Institution in Turkiye.

METHODS: This comparative, real-life, retrospective cohort study included treatment-naïve nAMD patients treated starting with three loading doses of IVB, switched to three loading doses of IVR and IVA due to treatment failure after IVB loading, and followed up one year with a treat-and-extend (T&E) protocol with 2-week extension/shortening intervals. The primary outcomes were changes in best-corrected visual acuity (BCVA; logMAR) and central macular thickness (CMT, μm) one year after the switch, and the secondary outcomes were maximum treatment intervals, number of injections, and disease activity rates.

RESULTS: The mean age (72.9±8.2 and 72.2±6.7, p=0.677) and gender (60.0% and 47.4% females, p=0.398) were similar among the IVR (35 eyes/patients) and IVA (38 eyes/patients) groups. The median BCVA and CMT were significantly improved during the study period (p<0.001) with no significant intergroup differences. The ratio of 4-, 6-, 8-, 10-, and 12-week maximum treatment intervals were 28.6%, 17.1%, 14.3%, 8.6%, and 31.4% in the IVR, and 13.2%, 15.8%, 21.1%, 15.8%, and 34.2% in the IVA group (p=0.492). The median (IQR) number of injections in the IVA group (8 [7–9]) was significantly lower than the IVR group (9 [8–12]) during the one-year T&E period (p=0.026). The disease activity rates were 34.3% and 26.4% one month (p=0.610) and 37.1% and 21.1% one year (p=0.195) after the switch in IVR and IVA groups.

CONCLUSION: This real-life comparison study indicates that, after the treatment failure with three loading doses of IVB, switching to either on-label anti-VEGF agent can be regarded as comparable considering functional and anatomical results. However, although maximum treatment intervals were not significantly different, fewer injections were required with aflibercept during the one-year T&E follow-up period.

Keywords: Aflibercept; age-related macular degeneration; bevacizumab; intravitreal injections; ranibizumab; wet macular degeneration.

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Several advances have been achieved in treating the potentially blinding primary retinal disease of neovascular age-related macular degeneration (nAMD) during the last two decades. With the introduction of intravitreal anti-vascular endothelial growth factors (anti-VEGFs), i.e., the gold standard treatment in nAMD, the disease has become manageable in which vision can be relatively preserved, even improved, with early intervention [1]. There are several anti-VEGF agents used intravitreally in nAMD treatment such as bevacizumab (Avastin® [Altuzan® in Turkiye], Genentech, CA, USA), ranibizumab (Lucentis®, Genentech, CA, USA), aflibercept (Eylea®, Regeneron, NY, USA), brolucizumab (Beovu®, Novartis Pharma AG, Basel, Switzerland) and faricimab (Vabysmo®, Genentech, CA, USA) [2]. However, only bevacizumab, ranibizumab, and aflibercept are currently available in Turkiye. Although all these mentioned drugs have US Food and Drug Administration (FDA) and European Medicine Agency (EMA) approval (on-label) for intravitreal use in nAMD, only bevacizumab, the first FDA (2004) and EMA (2005) authorized drug in the treatment of metastatic colon carcinoma, is used intravitreally without registration (off-label) for intraocular use [2].

The use of an off-label drug when there is an on-label alternative is generally discouraged due to ethical and legal concerns by several authorities [3, 4]. However, ophthalmological associations of some countries also encourage the use of off-label IVB as the first-line agent in several retinal diagnoses due to economic concerns and studies showing similar results in terms of effectiveness and side effect profiles [5–7]. In Turkiye, with an official notification published on December 28th, 2018, it became mandatory for treatment-naive nAMD patients to start their treatment with three doses of off-label intravitreal bevacizumab (IVB) in order to receive reimbursement from the Turkish Social Security Institution (SSI) [8]. Accordingly, the use of on-label anti-VEGF agents (i.e., intravitreal ranibizumab [IVR] and aflibercept [IVA]) is only included in the scope of reimbursement in case of treatment failure with IVB [8]. A recent survey study from Turkiye, involving 660 ophthalmologists who actively perform intravitreal injections, showed that 93.7% of them did not find it legally safe to use off-label IVB, but 55.9% were using IVB as first-line therapy in nAMD after SSI regulations [9]. The study also showed that this rate would decrease to 10.6% if these regulations did not exist [9].

Highlight key points

- In case of failure in treating neovascular age-related macular degeneration with off-label intravitreal bevacizumab, no difference was detected in terms of anatomical or functional results in switching to either intravitreal aflibercept or ranibizumab.
- Maximum intravitreal treatment intervals were not significantly different between ranibizumab and aflibercept during the one-year treat-and-extend follow-up period.
- After switching from bevacizumab, fewer injection numbers were needed during the one-year treat-and-extend protocol for neovascular age-related macular degeneration with aflibercept than with ranibizumab.

There are studies in the literature evaluating the treatment switch after treatment failure from IVB to IVR and IVA in nAMD separately [10–16]. Yet, deciding which agent to switch would be better for the patient and if there is a difference regarding efficacy remains a challenge with the limited available literature [17, 18]. Therefore, this real-life study aims to compare the one-year anatomical and functional results of switching to IVR or IVA after treatment failure with mandatory three-loading doses of IVB in nAMD at a tertiary center from Turkiye.

MATERIALS AND METHODS

This comparative, single-center, retrospective cohort study was conducted at Marmara University Faculty of Medicine, Department of Ophthalmology, Medical Retina Clinic, Istanbul, Turkiye. The study protocol was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (date: 03.02.2023, number: 09.2023.203). The study adhered to the latest amendments of the tenets of the Declaration of Helsinki and written informed consent provided by all of the patients at their first presentation to the clinic.

Study Population

Patients diagnosed with nAMD between January 2021 and January 2023 were retrospectively reviewed for eligibility. The study inclusion criteria were settled as being >50 years of age, diagnosed with nAMD, being treatment naïve, treatment initiation with three consecutive monthly doses of IVB injection, treatment failure after IVB loading doses, treatment switch to three consecutive monthly doses of an on-label anti-VEGF agent (IVR or IVA), treatment with treat-and-extend (T&E) protocol, and at least one year follow up after the switch.

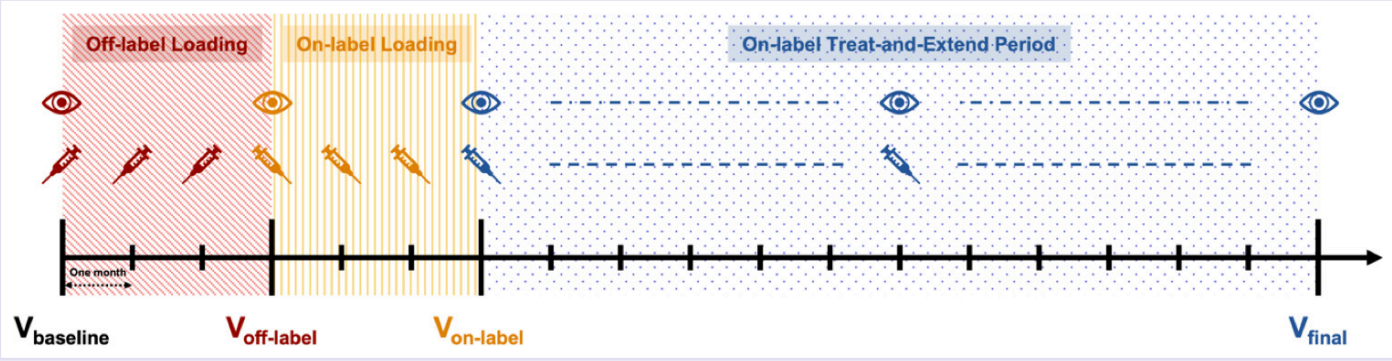

FIGURE 1. The schematic representation of the study timeline and study visits.

$V_{baseline}$, baseline visit; $V_{off-label}$, visit one month after the third loading dose of intravitreal bevacizumab injection; $V_{on-label}$, visit one month after the third loading dose of ranibizumab or aflibercept injection; V_{final}, the last visit of one-year treat-and-extend regimen with intravitreal ranibizumab or aflibercept injection.

The patients with intravitreal treatment before the study period, previous ocular surgery except for cataract extraction and intraocular lens implantation, visually significant cataract necessitating surgery during the study period, any retinopathy, any maculopathy other than nAMD, a deviation from the T&E protocol (defined as >7 days delay from the planned treatment interval), and any missing data were excluded from the study.

Patient Evaluations and nAMD Treatment

The patients had a comprehensive ophthalmologic examination, including the assessment of best-corrected visual acuity (BCVA) with an electronic Snellen chart, slit-lamp biomicroscopic anterior segment evaluation, dilated posterior segment and fundus examination, and spectral-domain optical coherence tomography (SD-OCT; Spectralis®, Heidelberg Engineering, Heidelberg, Germany) at all study visits (Fig. 1).

The diagnosis of nAMD was made by fundus examination and SD-OCT, and the disease activity was confirmed with fundus fluorescein angiography (Topcon TRC50DX; Topcon, Tokyo, Japan) in all cases at the baseline presentation visit ($V_{baseline}$). In the case of any suspect, polypoidal choroidal vasculopathy (PCV) was excluded by SD-OCT evaluation in enhanced depth imaging (EDI) mode and indocyanine green angiography (Topcon TRC50X; Topcon, Tokyo, Japan).

All patients were treated starting with three monthly loading doses of off-label IVB (1.25 mg/0.05 mL). At visit one month after the last loading IVB dose ($V_{off-label}$), the patient was evaluated for treatment failure according to predefined SSI criteria (no increase or decrease in BCVA compared to baseline, one line [5 letters] loss in BCVA, or a central macular thickness [CMT] of 250 µm and above in OCT evaluation) [8]. If one of the criteria mentioned above was met, the IVB treatment was considered a failure, and the off-label bevacizumab was switched to one of the on-label anti-VEGF agents (0.5 mg/0.05 mL ranibizumab or 2 mg/0.05 mL aflibercept). No specific criteria were used in the selection of on-label agents. Then, starting with the switch day, three monthly loading on-label agents were applied intravitreally, and the patient was re-evaluated at the visit one month after the last loading dose of the on-label agent ($V_{on-label}$). Then, the patient was followed up with a T&E protocol, including an administration of intravitreal on-label anti-VEGF agent at each visit with an extension of visit intervals by 2 weeks (to a maximum of 12 weeks) if the disease was inactive or a reduction of visit intervals by 2 weeks (to a minimum of 4 weeks) if the disease was active. The visit one year after the completion of the loading doses of on-label agents is considered the final visit of the study (V_{final}). All intravitreal injections were performed under sterile conditions in an outpatient operating room.

The Data

The demographical (age and sex) and clinical (BCVA, lens status as pseudophakic or phakic, anti-VEGF agent used, injection counts, maximum treatment intervals, disease activity, the presence of intraretinal [IRF] or subretinal fluid [SRF], central macular thickness [CMT; automatically calculated by the software of the SD-OCT device after manual foveal alignment], and any adverse events [subretinal hemorrhage, infectious or noninfectious endophthalmitis, retinal pigment epithelium tears, cardiovascular or cerebrovascular events]) characteristics of the patients were retrospectively collected from patient recordings and corresponding SD-OCT device.

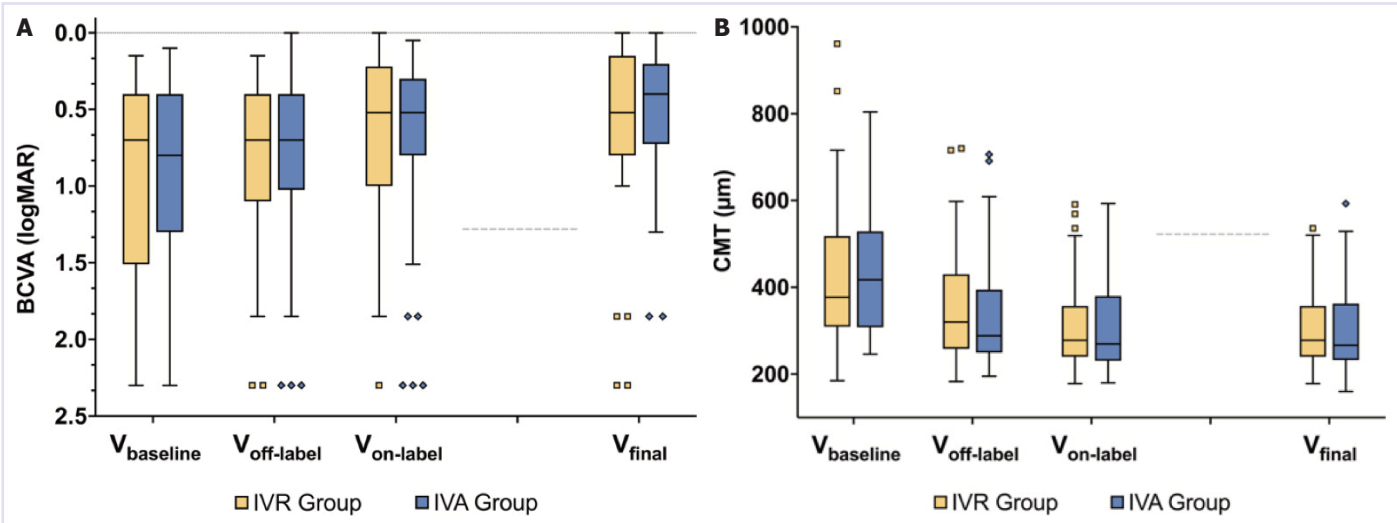

FIGURE 2. The box-plot graphs of best-corrected visual acuity **(A)** and central macular thickness **(B)** during the study period.

BCVA: Best corrected visual acuity; CMT: Central macular thickness; IVA: Intravitreal aflibercept; IVR: Intravitreal ranibizumab; logMAR: Logarithm of the minimum angle of resolution; $V_{baseline}$: Baseline visit; $V_{off\text{-}label}$: Visit one month after the third loading dose of intravitreal bevacizumab injection; $V_{on\text{-}label}$: Visit one month after the third loading dose of ranibizumab or aflibercept injection; V_{final}: The last visit of one-year treat-and-extend regimen with intravitreal ranibizumab or aflibercept injection. The dashed lines correspond to the treat-and-extend period.

Only one eye of each patient was included in the study analysis. If both eyes of the patient have nAMD, the study eye was randomly selected with an online integer generator (https://www.random.org/integers/). The nAMD was considered active if one of the qualitative criteria (presence of IRF, SRF, and subretinal hyperreflective exudate on SD-OCT and new retinal hemorrhage on dilated fundus examination) was met. Clinical and demographical characteristics of the patients who switched to intravitreal treatment with ranibizumab (IVR Group) and aflibercept (IVA Group) after IVB treatment failure were compared.

Statistical Analysis

The data analysis was employed by Statistical Package for the Social Sciences (SPSS) for macOS version 26.0 (IBM Corp., Armonk, NY, USA). The data distribution was determined by examination of histogram graphs and the Shapiro-Wilk test. Continuous variables with parametric and nonparametric distribution were given as mean±standard deviation (SD) and median (interquartile range [IQR]), respectively. The frequency (n) and percentage (%) values were given for categorical variables. For statistical analysis, BCVA obtained using the Snellen charts was converted to the logarithm of the minimum angle of resolution (logMAR) values. The logMAR equivalents for "counting fingers" at 5, 3, 2, and 1 meters and "hand motion" visual acuities were assumed to be 1.10, 1.30, 1.51, 1.85, and 2.30, respectively [19]. According to data distribution, quantitative data were compared using Mann-Whitney U or independent samples t-test between the study groups. Repeated measures among the study groups were compared using the Friedman test with post-hoc pairwise comparisons. Qualitative data were analyzed using the Pearson Chi-square or Fisher's exact test. Statistical significance was considered a two-sided p-value of less than 0.05, and Bonferroni-adjusted p-values were given where appropriate.

RESULTS

Thirty-five and 38 eyes of 35 and 38 patients in IVR and IVA groups were included in the study analysis, respectively. The mean age (72.9±8.2 and 72.2±6.7, p=0.677) and gender (20 [57.1%] and 18 [47.4%] females, p=0.484) of the patients were similar among the IVR and IVA groups, respectively. Twelve (34.3%) eyes in the IVR and 15 (39.5%) eyes in the IVA group were pseudophakic (p=0.809).

There was no significant difference in baseline BCVA and CMT between the study groups (p=0.786 and 0.855, respectively), and the median BCVA and CMT were significantly improved during the study period in both groups (p<0.001 for both groups). However, there were no significant differences in BCVA and CMT between the study groups at any follow-up visit (Table 1 and Fig. 2).

TABLE 1. The comparison of best-corrected visual acuity and central macular thickness between study groups during the study period

	Study visits				p[1]	p[2]	
	$V_{baseline}$ (a)	$V_{off\text{-}label}$ (b)	$V_{on\text{-}label}$ (c)	V_{final} (d)			
BCVA, logMAR							
IVR group					**<0.001**		
Mean±SD	0.9±0.6	0.8±0.6	0.7±0.6	0.6±0.6		a vs. b, 1.000	b vs. c, 0.426
Median (IQR)	0.7 (0.5–1.4)	0.7 (0.4–1.1)	0.5 (0.3–1.0)	0.5 (0.2–0.8)		a vs. c, 0.065	**b vs. d, 0.001**
Snellen equivalent	~20/100	~20/100	~20/40	~20/40		**a vs. d, <0.001**	c vs. d, 0.311
IVA group					**<0.001**		
Mean±SD	1.0±0.6	0.8±0.6	0.7±0.6	0.5±0.4		a vs. b, 0.453	b vs. c, 0.453
Median (IQR)	0.8 (0.4–1.3)	0.7 (0.4–1.0)	0.5 (0.3–0.8)	0.4 (0.2–0.7)		**a vs. c, 0.002**	**b vs. d, 0.002**
Snellen equivalent	~20/125	~20/100	~20/40	~20/50		**a vs. d, <0.001**	c vs. d, 0.453
p[3]	0.786	0.982	0.794	0.969	–	–	
CMT, µm					**<0.001**	a vs. b, 0.140	**b vs. c, 0.003**
IVR group	423.6±168.7	362.1±138.7	319.4±110.9	311.0±99.2		**a vs. c, <0.001**	**b vs. d, 0.001**
Mean±SD	377.0 (311.5–513.5)	320.0 (260.0–427.5)	278.0 (241.5–351.0)	278.0 (243.0–350.0)		**a vs. d, <0.001**	c vs. d, 1.000
Median (IQR)							
IVA group					**<0.001**	**a vs. b, 0.004**	b vs. c, 0.068
Mean±SD	425.5±144.6	345.0±133.9	306.5±101.1	299.7±105.5		**a vs. c, <0.001**	**b vs. d, 0.010**
Median (IQR)	417.0 (308.0–528.0)	288.5 (251.0–379.0)	269.5 (231.0–378.0)	266.5 (235.0–257.0)		**a vs. d, <0.001**	c vs. d, 1.000
p[3]	0.855	0.529	0.687	0.497	–	–	

BCVA: Best corrected visual acuity; CMT: Central macular thickness; IVA: Intravitreal aflibercept; IQR: Interquartile range; IVR: Intravitreal ranibizumab; logMAR: Logarithm of the minimum angle of resolution; SD: Standard deviation; $V_{baseline}$: Baseline visit; $V_{off\text{-}label}$: Visit one month after the third loading dose of intravitreal bevacizumab injection; $V_{on\text{-}label}$: Visit one month after the third loading dose of intravitreal ranibizumab or aflibercept injection; V_{final}: The last visit of one-year treat-and-extend regimen with intravitreal ranibizumab or aflibercept injection; p1: Friedman test; p2: Post hoc analysis with pairwise comparisons, adjusted with Bonferroni correction; p3: Mann-Whitney U test. Bold values indicate statistical significance.

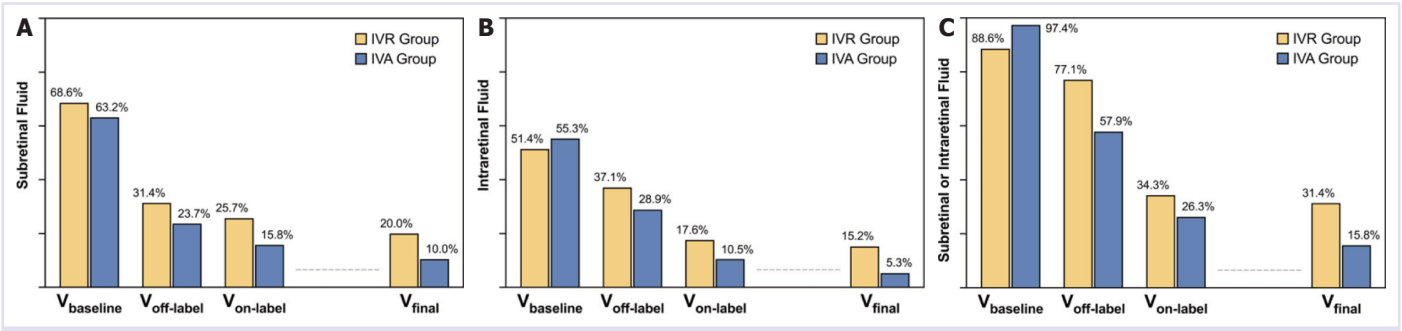

Figure 3. The subretinal **(A)**, intraretinal **(B)**, and subretinal or intraretinal fluid **(C)** ratio of the study groups during the study period.

IVA: Intravitreal aflibercept; IVR: Intravitreal ranibizumab; $V_{baseline}$: Baseline visit; $V_{off\text{-}label}$: Visit one month after the third loading dose of intravitreal bevacizumab injection; $V_{on\text{-}label}$: Visit one month after the third loading dose of ranibizumab or aflibercept injection; V_{final}: The last visit of one-year treat-and-extend regimen with intravitreal ranibizumab or aflibercept injection. The dashed lines correspond to the treat-and-extend period.

All eyes had active nAMD lesions at baseline and $V_{off\text{-}label}$. The disease activity rates were not significantly different between IVR and IVA groups at $V_{on\text{-}label}$ (12 [34.3%] and 10 [26.4%] eyes, p=0.610) and V_{final} (13 [37.1%] and 8 [21.1%] eyes, p=0.195), respectively. The rates of SRF, IRF, and SRF or IRF at the study visits were given in Figure 3. There were no significant differences between the study groups regarding SRF, IRF, and SRF or IRF rates.

The maximum treatment intervals among the study groups were not significantly different (p=0.492) (Fig. 4); however, the median number of intravitreal injections in the IVA group (8.0 [7.0–9.0] injections) was significantly lower than the IVR group (9.0 [8.0–12.0] injections) during the T&E period (p=0.026). The number of injections was also significantly lower in the IVA (11.0 [10.0–12.0] injections) than the IVR (12.0 [11.0–15.0] injections) group when including the loading period of the T&E regimen (p=0.026).

No adverse events were observed during the study period in the study groups.

DISCUSSION

This single-center retrospective cohort study investigating the switch to an on-label intravitreal anti-VEGF after obligatorily starting with off-label IVB due to reimbursement guidelines of SSI in Turkiye demonstrated comparable one-year anatomical and functional results either with T&E IVR or IVA; however, with fewer injection numbers using IVA. This is the first study assessing whether the selected on-label anti-VEGF agent makes a difference in case of IVB treatment failure after three-loading doses according to a treatment initiation protocol of Turkiye on its own.

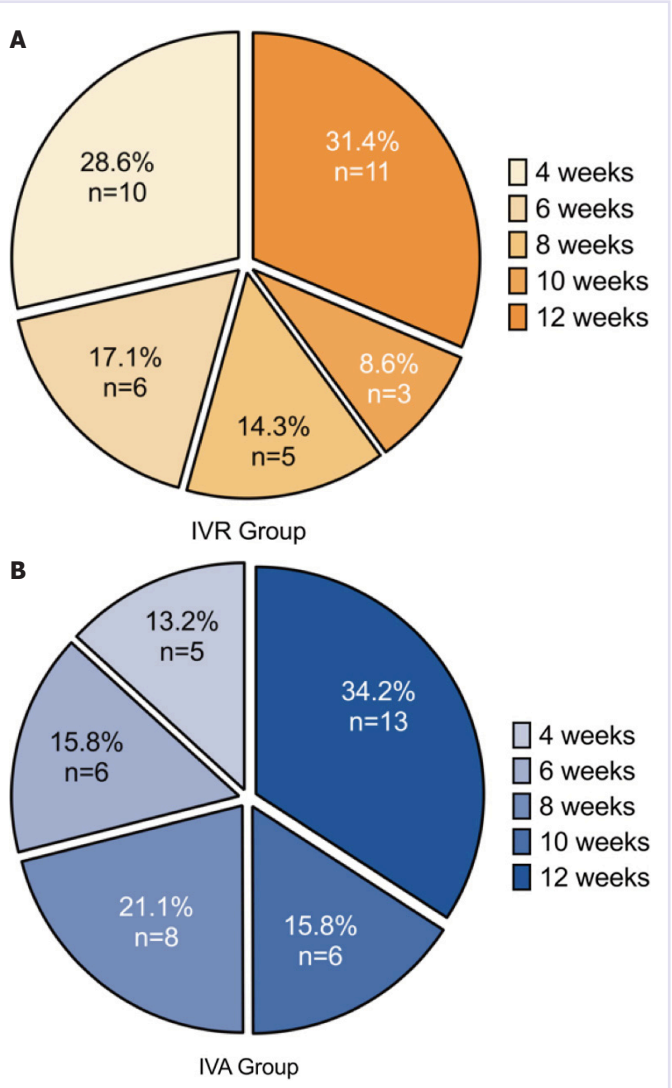

Figure 4. Maximum treatment intervals of the study groups during the treat-and-extend period.

IVA: Intravitreal aflibercept; IVR: Intravitreal ranibizumab.

Recent meta-analyses of randomized controlled trials (RCTs) showed that T&E regimens in nAMD have the advantages of fewer injections and fewer clinic visits compared to monthly and pro re nata (PRN) protocols, respectively, with no significant difference in efficacy and safety measures [20]. However, diverse criteria to shorten, maintain, or extend the treatment intervals and different interval lengths applied in those studies make comparing different anti-VEGF agents controversial unless directly compared during the same study [21]. The only RCT directly comparing IVR and IVA in nAMD on a T&E regimen was the 2-year, multicenter, phase IV study of RIVAL from Australia [22]. In this study, treatment-naïve nAMD patients were randomly allocated to IVR and IVA treatment arms and followed up in a T&E protocol with a predefined extension, shortening, and maintenance criteria after three-monthly loading doses [22]. In our study, although treatment decisions were not strictly controlled with a reading center due to its real-life nature, the T&E guideline applied in our clinic was standardized with three criteria: shorten the treatment interval by 2 weeks (to a minimum of 4 weeks) if there is an active lesion (i.e., any IRF, SRF, subretinal hyperreflective exudate, or new hemorrhage), extend the interval by 2 weeks (to a maximum of 12 weeks) if no sign of disease activity, and no maintenance of treatment intervals. Therefore, extension and shortening decisions made on a patient basis can be considered homogenous for both intravitreal agents during the study period.

The primary endpoint of the RIVAL was the development of macular atrophy amongst the patients treated with IVR or IVA [22]. However, the preplanned interim analysis revealed comparable mean BCVA changes (6.9±12.3 and 5.2±12.8 BCVA logMAR letter score), approximate Snellen equivalent visual acuities (20/32 and 20/40), and estimated mean number of injections (11.2 [95% confidence interval [CI], 10.9–11.5] and 11.5 [95% CI, 10.8–11.5]) between IVR and IVA groups at 12-months, respectively [23]. The secondary outcome measures of the 24-month completed study of RIVAL also revealed similar BCVA gains and injection numbers with IVR and IVA [22]. Similarly, we found comparable BCVA between IVR and IVA groups during the study period, with lower final approximate visual acuities (20/40 and 20/50, respectively) than the RIVAL study. This could have resulted from the lower presenting BCVA of patients in our study since no exclusion criteria regarding visual acuities were applied considering its real-life design. Conversely, we found a significantly lower number of injections with IVA compared to IVR, which the lack of interval-maintaining criteria in our T&E protocol could explain. Also, in the RIVAL study, five or more letters of visual acuity loss from the BCVA recorded since treatment initiation was considered a disease activity criterion [22, 23]. This could also have influenced the treatment intervals by different distribution of activity criteria amongst the study groups, resulting in similar injection numbers.

A recent prospective case series from Brazil involving the two-year head-to-head comparison of T&E IVB, IVR, IVA, and intravitreal ziv-aflibercept (an off-label aflibercept molecule with higher osmolarity registered as chemotherapeutic for metastatic colorectal carcinoma) also demonstrated similar visual acuity gains with lower injection numbers using IVA compared to other agents, supporting the findings of our study [24]. Although the maximum injection interval differences did not reach statistical significance in our study, the percentage of treatment interval of 4 weeks was higher in the IVR (28.6%) than in the IVA (13.2%) group. This could be interpreted as a potential clinical importance of IVA for certain patients while lowering the burden of treatment, together with the available literature supporting longer injection intervals with fewer injection numbers when IVA switched from IVB or IVR [14, 15, 25–28].

Studies directly comparing the anatomical or functional results of switching from IVB to IVR or IVA in treating nAMD are limited in the literature. First, to our knowledge, Waizel et al. [17] reported a substantial anatomical benefit from switching to either IVR or IVA after a mean of 10.5±7.6 (range, 3–33) IVB injections, with a minimal functional improvement sightly favoring IVA (~1.0 line) to IVR (~0.4 lines). A retrospective single-center study from Mexico also compared the single-dose CMT change results of switching to IVR and IVA after a mean of 5.8 (range, 1–18) and 6.0 (range, 1–18) IVB injections, demonstrating robust but comparable results between the anti-VEGF agents [18]. Our results seem comparable to those studies regarding further improvement in CMT with switch, and no significant differences between the IVR and IVA groups.

The limitations of the inherent retrospective design and the relatively small sample size of this study should be considered while interpreting its results. Additionally, the duration of nAMD in the eyes before treatment was not evaluated. Nevertheless, as a reflection of real-life practice, its single-center design with joint treatment protocol and homogenous intervention groups could be regarded as the strengths of the study.

Conclusion

Whether mandated by social security institutions, imposed as step therapy by insurers, or preferred by patients due to financial difficulties, the utility of off-label intravitreal anti-VEGF agents is a fact in low-income countries such as Turkiye. However, the literature has limited data about which on-label agent to switch after an off-label anti-VEGF in nAMD patients. This real-life study indicates that in case of treatment failure after three intravitreal loading doses of bevacizumab, switching either to ranibizumab or aflibercept can be considered comparable regarding anatomical and functional results. Future RCTs may provide a guide on this subject.

Ethics Committee Approval: The Marmara University Clinical Research Ethics Committee granted approval for this study (date: 03.02.2023, number: 09.2023.203).

Authorship Contributions: Concept – MOS, NZT, AA, DDY, OS; Design – MOS, NZT, AA, DDY, OS; Supervision – MOS, NZT, AA, DDY, OS; Fundings – MOS, OS; Materials – MOS, NZT, OS; Data collection and/or processing – MOS, NZT; Analysis and/or interpretation – MOS, NZT, AA, DDY, OS; Literature review – MOS, NZT, DDY; Writing – MOS, NZT; Critical review – MOS, NZT, AA, DDY, OS.

Conflict of Interest: No conflict of interest was declared by the authors.

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