Original Article

Results of the Switch from Intravitreal Ranibizumab to Intravitreal Aflibercept Therapy in Patients with Neovascular Age-Related Macular Degeneration: A 42-month Retrospective Real-World Study

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Received: 28-Dec-2020;
Revision: 04-Apr-2021;
Accepted: 22-Jun-2021;
Published: 09-Dec-2021

ABSTRACT

Aim: The study aimed to evaluate the functional and anatomical results of patients treated with intravitreal ranibizumab (IVR) for neovascular age-related macular degeneration (n-AMD) but switched to intravitreal aflibercept (IVA) treatment due to insufficient response treatment. **Material and Methods:** At least six doses of n-AMD were administered IVR to 33 patients who were switched to IVA treatment due to insufficient response and were included in the study. The patients were evaluated at the beginning of the IVR treatment during the transition to IVA treatment and at 6, 12, 18, 24, 30, 36, and 42 months of IVA treatment. **Results:** After an average of 10.1 ± 5.04 IVR injections, the patients who were accepted as insufficient response were treated with IVA. The central macular thickness of the patients was evaluated at the beginning of the treatment, immediately before, and after the initiation of IVA treatment at 6, 12, 18, 24, 30, 36, 42 months. It was as follows: 325.21 ± 123.04, 351.42 ± 126.09, 284.81 ± 112.65, 296.68 ± 89.17, 282.61 ± 81.58, 292.27 ± 109, 92,269.75 ± 97.14, 267.50 ± 87.56, and 266.82 ± 88.35 μm. According to the best-corrected visual acuity (BCVA), it was initially 0.89 ± 0.65; 1.08 ± 0.53 during the transition to IVA; 0.91 ± 0.46 6 months after IVA; 12th 1.14 ± 0.59; 0.94 ± 0.55 at 18th; 1.07 ± 0.49 at 24th; 1.15 ± 0.57 at 30th; 1.06 ± 0.45 at 36th, and 1.13 ± 0.46 LogMAR (Logarithm of the Minimum Angle of Resolution) at the 42nd month. **Conclusion:** In conclusion, in n-AMD patients with inadequate response to intravitreal ranibizumab or with relapse, and therefore, switched to aflibercept treatment, the anatomical improvement and sustainment were observed, however, functional recovery could not be achieved.

KEYWORDS: *Aflibercept, age-related macular degeneration, ranibizumab, switch*

INTRODUCTION

Age-related macular degeneration (AMD) is one of the top causes of irreversible blindness among people aged 50 years or older worldwide.[1] In AMD, the growth of new choroidal vessels in the macula caused by vascular endothelial growth factor (VEGF) and vascular leakage may result in vision loss.[2] Severe visual loss may occur in the neovascular form of the disease consisting of abnormal development of new blood vessels under or within the central region of the retina. While the underlying pathological mechanisms of neovascularization are not fully clear, VEGF-A, which plays a role in angiogenesis and vascular permeability, has been associated with neovascularization.[3] Therefore, intravitreal administration of anti-VEGF agents has become the standard treatment for neovascular AMD (n-AMD).[4] Ranibizumab was the first to demonstrate the effectiveness of intravitreal anti-VEGF agents in n-AMD treatment. Monthly injections or pro re nata (PRN) ranibizumab treatment

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_696_20

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How to cite this article: Ertan E, Efe N, Sabaner MC, Doğan M. Results of the switch from intravitreal ranibizumab to intravitreal aflibercept therapy in patients with neovascular age-related macular degeneration: A 42-month retrospective real-world study. Niger J Clin Pract 2021;24:1824-7.

hindered visual loss and even increased visual acuity (VA) in some patients.[5] Compared to other anti-VEGF agents, aflibercept is a novel fusion protein that binds both the VEGF and placental growth factor.[6] Studies have shown that an aflibercept injection every 8 weeks and monthly ranibizumab treatment maintain similar VA.[7] One meta-analysis showed that aflibercept yielded positive anatomical results in patients resistant to previous treatments with other anti-VEGF agents.[8] Although the treatment protocols varied among different studies, monthly injection fixed-interval treatment protocol or PRN injections upon active symptoms were implemented in most of the prior studies.[5,9,10] In this study, visual and anatomical outcomes of switching from ranibizumab to aflibercept therapy were measured in patients with n-AMD at 42 months.

Material and Methods

Medical records of all patients diagnosed with n-AMD who were treated at our hospital, a tertiary care clinic, retina center, between January 2014 and June 2019 were retrospectively reviewed. Patients with a known diagnosis of n-AMD who were resistant to intravitreal ranibizumab injection with PRN regimen and switched to aflibercept treatment were included in the study.

Inclusion criteria for our study were as follows: Presence of n-AMD previously treated with intravitreal ranibizumab which was switched to intravitreal aflibercept, persistent intraretinal or subretinal fluid, minimum of six ranibizumab injections with PRN regimen before the transition, a final injection of ranibizumab 28–35 days within switching to aflibercept, and at least 42 months of follow-up after switching to aflibercept.

Exclusion criteria were as follows: History of vitrectomy, choroidal neovascularization (CNV) lesions secondary to causes other than AMD; the presence of −6.00 D or greater myopia; and uncontrolled glaucoma, uveitis, or any other ocular disease that could potentially confound the assessment of safety and/or efficacy of treatment.

The study included a total of 33 eyes of 33 patients. The presence of resistant and/or recurrent subretinal and/or intraretinal fluid was accepted as the indication for transition to aflibercept despite at least six doses of ranibizumab. During the monthly follow-up period, the patients underwent complete ophthalmologic examinations including best-corrected visual acuity (BCVA) with using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, intraocular pressure (IOP) measurement, fundus examination, and spectral-domain optical coherence tomography (SD-OCT, Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) scanning.

After switching from ranibizumab (IVR), all the patients received a loading dose of three monthly aflibercept injections (IVA) (2 mg/0.05 mL), and received a monthly follow-up. Retreatment with a single aflibercept injection was performed according to any of the following: VA loss of at least five letters with SD-OCT evidence of fluid in the macula, persistent or recurrent intraretinal or subretinal fluid in SD-OCT, or new subretinal hemorrhage from CNV.

The demographic characteristics of the patients were recorded. The main outcomes of the study were variations of BCVA and central macular thickness (CMT) after switching to aflibercept at months 0, 6, 12, 18, 30, 36, and 42 and the frequency of aflibercept injections.

SPSS version 18.0 (Chicago, USA) statistical package program was used for data analysis. Shapiro–Wilk's test was used to assess the distribution of the variables. Paired *t*-test was used to compare the parametric data measured before and during the injections. Wilcoxon 2-Related samples test was used to compare the nonparametric measurements obtained before and during the injections. Spearman's test was used to determine the correlations between the changes in the CMT, BCVA, and the number of injections at the end of 42 months. Evaluations were made at a 95% confidence interval, and $P < 0.05$ was considered statistically significant.

Our study obtained ethics approval from the Afyon Kocatepe University, Clinical Research Ethical Committee (2011-253) and was conducted in accordance with the Declaration of Helsinki. All the study participants provided informed written consent.

Results

The inclusion criteria were met by 33 eyes. The mean patient age was 71.57 ± 7.98 years (61–89 years) [Table 1]. In total, 21 (63%) patients were males and 12 (37%) were females. After mean 10.1 ± 5.04 IVR injections, patients considered to have insufficient response were switched to IVA. CMT was measured at the start of the treatment and immediately before and after the initiation of IVA treatment at 6, 12, 18, 24, 30, 36, and 42 months as follows:

Table 1: Demographics of the study groups

	Patients with AMD (Mean±SD) (*n*: 33)
Age (year)	71.56±7.98
Male:Female ratio	21:12
IVR injection before switch	10.1±5.04
IVA injection after switch	12.96±1.63

AMD: Age-related macular degeneration; IVR: Intravitreal ranibizumab; IVA: Intravitreal aflibercept

Table 2: Central macular thickness and best-corrected visual acuity parameters analysis between measurements

	CMT (µm) (Mean±SD) (*n*: 33)	*P**	BCVA (LogMAR) (Mean±SD) (*n*: 33)	*P*⁺
Beginning	325.21±123.04	-	0.89±0.65	-
Switch	351.42±126.09	0.344	1.08±0.53	**0.043**
6th month	284.81±112.65	0.066	0.91±0.46	0.418
12th month	296.68±89.17	0.223	1.14±0.59	**0.003**
18th month	282.61±81.58	0.095	0.94±0.55	0.485
24th month	292.27±109.92	0.228	1.07±0.49	**0.019**
30th month	269.75±97.14	**0.029**	1.15±0.57	**0.016**
36th month	267.50±87.56	**0.039**	1.06±0.45	**0.034**
42nd month	266.82±88.35	**0.034**	1.13±0.46	**0.024**

*: Parametric paired samples test, ⁺: Nonparametric Wilcoxon 2-related sample test results with comparison from beginning measurement: *P*<0.05 was considered statistically different and was indicated as bold. CMT: Central macular thickness, BCVA: Best-corrected visual acuity

325.21 ± 123.04, 351.42 ± 126.09, 284.81 ± 112.65, 296.68 ± 89.17, 282.61 ± 81.58, 292.27 ± 109.92, 269.75 ± 97.14, 267.50 ± 87.56, and 266.82 ± 88.35 µm, respectively [Table 2]. BCVA LogMAR was initially 0.89 ± 0.65, 1.08 ± 0.53 during the transition to IVA, 0.91 ± 0.46 6 months after IVA; 1.14 ± 0.59 at 12 months, 0.94 ± 0.55 at 18 months, 1.07 ± 0.49 at 24 months, 1.15 ± 0.57 at 30 months, 1.06 ± 0.45 at 36 months, and 1.13 ± 0.46 at 42 months.

There was no correlation between the changes in CMT and the number of injections (P = 0.878, r = -0.029), changes in BCVA and number of injections (P = 0.875, r = 0,029), or changes in CMT and BCVA (P = 0.321, r = 0.184) at the end of 42 months compared to the start of the treatment.

Systemic complications such as cardiovascular or cerebrovascular events or ocular complications such as endophthalmitis, vitreous hemorrhage, retinal detachment, or sustained IOP increase were not observed throughout the study period.

Discussion

Within the scope of the study, n-AMD patients with insufficient response to ranibizumab were switched to intravitreal aflibercept treatment in which macular anatomical improvement was preserved or sustained throughout the 42-month follow-up period. At the end of 42 months, VA decreased while the anatomical structure was preserved. However, there was no correlation between improvement in VA and anatomical improvement. Similar to our results, Spooner *et al*.[11] and Cardoso *et al*.[12] observed a significant anatomical effect, resulting in CRT thinning, but found no association with VA improvement. Other studies have demonstrated positive anatomical results in the eyes that were resistant to other anti-VEGF treatments and switched to aflibercept.[13-15] Aflibercept also binds Placental growth factor (PlGF) and shows a greater binding affinity to VEGF compared to other anti-VEGF agents, which may be one of the reasons behind this positive effect.[6] In addition, repeated bevacizumab or ranibizumab injections have been shown to cause immunoreactivity against mouse-derived humanized monoclonal antibodies and/or loss of therapeutic effect and tachyphylaxis. The treatment can be interrupted for a short time in order to regain drug efficacy.[16,17] Switching to aflibercept may also improve contrast sensitivity as well as vision-related quality of life despite the lack of changes in BCVA.[18] Long-term ranibizumab therapy may also lead to tolerance, which may also reduce drug efficacy over time, however, unlike tachyphylaxis, efficacy is not recoverable by discontinuation of treatment.[19] In our study, as in other studies, that achieved similar results, one of the advantages of aflibercept was that the average number of injections used in the aflibercept treatment was lower than in the ranibizumab treatment in the same period.[20,21] According to the results of the studies, there is no consensus on the impact of switching from ranibizumab to aflibercept treatment on VA.[15,22,23] Long-term ranibizumab treatment risks of geographic atrophy, chronic structural changes in the macula, and loss of foveal photoreceptors may be the reasons causing inconsistency between anatomical and visual outcomes.[24] Controlling the formation of CNV-induced intraretinal or subretinal fluid with IVA injections, and persistence of injections may have affected CMT values at the 42-month follow-up. We believe that functional improvement is unassociated with anatomical improvement due to CNV-induced scar formation, and therefore, there is no correlation between the number of injections and BCVA. The safety of aflibercept has been well-established and has not shown inferiority to ranibizumab.[7] Significant incidences of adverse events that may be associated with aflibercept were not observed. The limitations of our study may be considered to be the lack of a control group and the lower number of patients. A long-term follow-up of the patients is vital for contributing in a study. Incomplete response

to anti-VEGF therapy demonstrates the multifactorial pathophysiology of AMD. The refractory quality of these eyes may be reflected by the lack of sustained visual improvement, and the chronic disease course may be manifested as a ceiling effect of anti-VEGF therapy.

Conclusion

In conclusion, in n-AMD patients with inadequate response to intravitreal ranibizumab or with relapse, and therefore switched to aflibercept treatment, anatomical improvement, and sustainment were observed, however, functional recovery could not be achieved.

Ethical approval

The study adhered to the tenets of the Declaration of Helsinki. Local ethics committee of clinical research approved the study protocol.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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