• Clinical Research •

Treatment results switching from aflibercept to bevacizumab in wet age-related macular degeneration

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Abstract

● **AIM:** To examine effects of switching intravitreal aflibercept to bevacizumab in neovascular age-related macular degeneration (nAMD).

● **METHODS:** Data from patients treated for nAMD with anti-vascular endothelial growth factor (VEGF) injections at Örebro University Hospital between January 2014 and June 2020, were extracted from the Swedish macular register (SMR). A total of 230 eyes were included in the study: 116 in the study/bevacizumab switch group and 114 in the control/aflibercept group. Central retinal thickness (CRT) was measured at baseline and after 2y. Primary outcome was mean change in best corrected visual acuity (BCVA) between baseline and 2y. Secondary outcome variables included proportion of patients with a clinically significant change in BCVA [increase or decrease of ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters], mean change in CRT, number of anti-VEGF injections, number of visits assessing disease activity and number of visits with active disease.

● **RESULTS:** The mean difference in BCVA between baseline and 2y was 1.13±14.47 ETDRS letters in the bevacizumab switch group and 1.81±13.01 ETDRS letters in the aflibercept group. The lower bound of the 95% confidence interval of the difference in BCVA was -4.25, indicating non-inferiority within a 5 ETDRS letter limit. No significant differences in mean change of CRT between baseline and 2y were detected (study -185.9±167.0 versus control -149.4±193.1 μm, *P*=0.127). The distribution of clinically significant improvement (*P*=0.598) or worsening (*P*=0.508) of BCVA during follow-up did not show statistically significant differences between groups. The number of anti-VEGF injections administered (study 12.76±2.20 versus control 13.10±4.20, *P*=0.442), the number of visits assessing disease activity (*P*=0.301), and the number of visits with active disease (*P*=0.065) did not show differences between subjects receiving bevacizumab and aflibercept treatment. No significant differences were detected in baseline characteristics between the study and control groups, including age, BCVA, CRT, neovascular membrane type or location, duration of symptoms or prior cataract surgery.

● **CONCLUSION:** Switching to off-label bevacizumab in patients responding to initial aflibercept treatment is non-inferior to continued aflibercept treatment with respect to change in visual acuity at 2y. Switching anti-VEGF from aflibercept to bevacizumab may be a viable option in clinical settings with limited resources.

● **KEYWORDS:** age-related macular degeneration; anti-vascular endothelial growth factor; bevacizumab; aflibecept
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INTRODUCTION

Age-related macular degeneration (AMD) is a prevalent eye condition and a leading cause of vision loss and image distortion in individuals over 50 years of age. It is a major health concern affecting nearly 200 million people worldwide, as well as an important socio-economic burden[1]. AMD is classified into a dry (atrophic) and a more aggressively progressing neovascular form. Dry AMD is the more common form accounting for about 85%-90% of cases, and is characterized by drusen deposition and atrophy. Neovascular AMD (nAMD), though less common, is more severe and rapidly progressing. It is characterized by neovascular ingrowth under the retina, leading to fluid leakage and hemorrhage[2]. Vascular endothelial growth factor (VEGF) is involved in the pathophysiology of nAMD, and since intravitreal anti-VEGF therapy was first introduced in 2004, it has revolutionized the

treatment of nAMD[3]. A significant reduction in morbidity and blindness due to nAMD has been shown as anti-VEGF treatment protocols have been almost universally adopted[4]. The most commonly used anti-VEGFs for treating nAMD are aflibercept, ranibizumab, bevacizumab and brolucizumab[5]. Recently a new anti-VEGF drug, faricimab, has been approved for the treatment of nAMD[6].

Bevacizumab is a recombinant humanised monoclonal antibody with affinity to all biologically active isoforms of VEGF-A[7]. Aflibercept is a decoy receptor fusion protein with a high affinity for VEGF-A, VEGF-B, and placental growth factor[8]. Aflibercept and ranibizumab are both approved for treating nAMD. Although widely used in clinical practice, bevacizumab is currently not approved by any health authority for the treatment of nAMD[5]. Studies to date have not been able to show meaningful differences in visual acuity between bevacizumab, ranibizumab and aflibercept[9-10].

Several Meta-analyses have shown anti-VEGF treatment to be cost-effective compared to no treatment or earlier nAMD therapies (laser photocoagulation and photodynamic therapy)[11]. Among the different anti-VEGF drugs available, bevacizumab is consistently identified as the most cost-effective one, with estimates of overspending €335 million on a European scale compared to aflibercept[12-13].

Tachyphylaxis has been proposed as a possible mechanism in patients developing late non-response to anti-VEGF drugs[14-15]. Many studies have investigated the effect of changing from bevacizumab or ranibizumab to aflibercept, in nAMD patients with unsatisfactory results with first line therapy. Visual acuity and anatomical results after switching to aflibercept have been inconsistent[16-19]. Only a few smaller studies have examined the effects of changing aflibercept or ranibizumab to off-label bevacizumab in nAMD[20-21].

Aflibercept was introduced in Sweden in 2013, and was the main anti-VEGF used in treatment-naïve nAMD patients at Örebro University Hospital, between 2014 and 2017. In 2017, the nAMD treatment protocol was changed in order to cut drug/anti-VEGF costs. All patients responding to initial treatment (4 injections) with aflibercept were switched to bevacizumab from the fifth injection on, using a treat-and-extend regimen (TER).

The studies to date examining switching anti-VEGF to bevacizumab are small, lack control groups and have relatively short follow-up periods. We are not aware of any previous publications assessing visual acuity and anatomical outcome after systematically switching aflibercept to bevacizumab.

The objective of this study is to retrospectively compare visual acuity and central retinal thickness (CRT) results in nAMD patients switching to off-label bevacizumab versus continued aflibercept treatment in a real world setting.

PARTICIPANTS AND METHODS

Ethical Approval The study was designed as a retrospective, cross-sectional, observational study. Data were extracted from the SMR on all eyes receiving anti-VEGF treatment for nAMD at Örebro University Hospital between January 2014 and June 2020. The study protocol was approved by the institutional review board (decision number 2019-06140) and was conducted in conformity with the Helsinki Declaration.

The Swedish macular register (SMR) is a national quality register for macular diseases, with 48 eye clinics currently entering data. In 2015 it included 84% of patients treated for nAMD in Sweden. All patients receiving anti-VEGF treatment at Örebro University Hospital are entered into the SMR. Informed consent is received before entering data into the register. Information collected from each visit includes clinic, visit date, patients' age and sex, duration of symptoms at diagnosis, macular lesion type and location, best corrected visual acuity (BCVA), best- or worse-seeing eye treated, treatment drug, number of injections, and adverse events[22].

At the time of the study, all patients with suspected nAMD at Örebro University Hospital were routinely examined with spectral domain optical coherence tomography (OCT) and fluorescein and/or indocyanine green angiography, unless contraindications were present. The diagnosis of nAMD was confirmed by a medical retina specialist and patient consent was acquired before starting intravitreal anti-VEGF treatment. The Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart was used for measuring visual acuity. Figure 1 summarizes the TER treatment protocol for treatment-naïve nAMD patients at Örebro University Hospital, at the time of the study. Patients initially received three monthly doses of aflibercept with an extension of the control/treatment interval to 2mo after the last dose. If treatment response to aflibercept had been achieved, another dose of aflibercept was administered (4^{th} dose) and the treatment interval was kept at 8wk. From the fifth injection on (at 6mo from baseline) patients from 2017 and onwards switched to bevacizumab. The treatment intervals were extended according to TER, with a maximum treatment interval of 12wk and a minimum interval of 4wk. Patients with a very poor prognosis (very low visual acuity at baseline or poor compliance), could receive treatment according to other protocols or using other anti-VEGF agents, at the discretion of their treating medical retina specialist. These patients, along with non-responders to initial aflibercept treatment, were not eligible for our study.

Information on age, BCVA (baseline, 1 and 2y), neovascular membrane type and localization, duration of symptoms, number of anti-VEGF injections, and prior cataract surgery were acquired from the SMR data. Patients were entered into the SMR when starting anti-VEGF therapy. Data from eligible

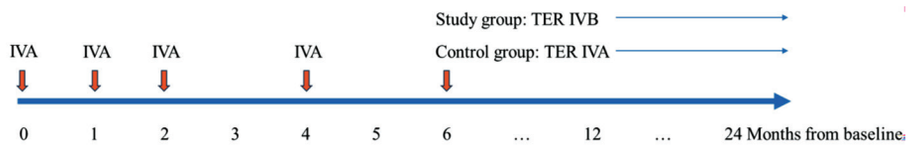

Figure 1 Summary of treatment protocol for nAMD nAMD: Neovascular age-related macular degeneration; TER: Treat-and-extend regimen; IVA: Intravitreal aflibercept; IVB: Intravitreal bevacizumab.

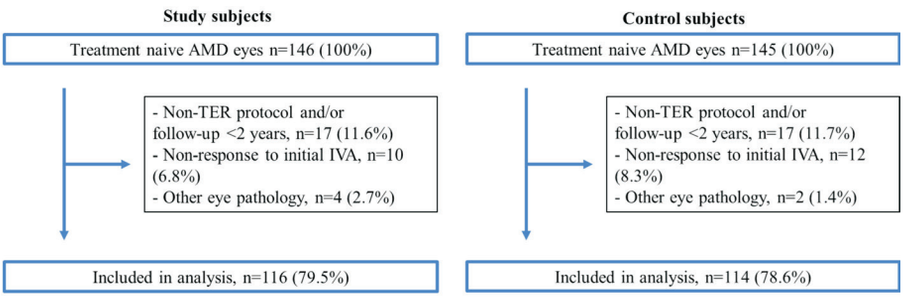

Figure 2 Summary of inclusion of study and control subjects AMD: Age-related macular degeneration; TER: Treat-and-extend regimen; IVA: Intravitreal aflibercept therapy.

subjects were collected up to the first visit occurring after 24mo. The treatment protocol used, the number of control visits, the number of control visits with active disease, and instances of cataract surgery during follow-up were collected from electronic patient charts.

CRT was measured manually from OCT images acquired at baseline, 1, and 2y visits. CRT was defined as the distance between internal limiting membrane and the Bruch's membrane at the center of fovea.

Treatment response was defined as the absence of intra- or subretinal fluid, pigment epithelial detachment, or significant visual loss (>5 ETDRS letters).

The SMR data were used to identify the study and control groups. Inclusion criteria included treatment-naïve nAMD, treated according to TER protocol with initial aflibercept treatment, treatment response at 2 and 4mo (=eligible for extending treatment interval and bevacizumab switch) and a follow-up of at least 24mo. Exclusion criteria included other macular pathology, or sight threatening disease other than cataract.

The study group included treatment-naïve nAMD eyes enrolled in the SMR, starting anti-VEGF therapy from January 1st to December 31st, 2017. Of the 146 eyes entered into the register during the year, 27 (18.5%) did not meet the inclusion criteria. Four eyes had other eye pathologies and were excluded (2 eyes with glaucoma, 1 with epiretinal membrane and 1 with macular hole). Thus, 116 subjects (79.5% of the total) were included in the analysis. The control group similarly included treatment-naïve nAMD eyes starting anti-VEGF therapy between January 1st and December 31st, 2014. Of 145 eyes, 29 (20%) did not meet the inclusion criteria. A total of 114 eyes (78.6%) were included for analysis after exclusion of 1 eye with glaucoma and 1 with an epiretinal membrane. Figure 2 Summarizes the inclusion of subjects to the study and control cohorts. Totally 230 eyes (116 in bevacizumab switch group and 114 in aflibercept group) were included in the study. The primary outcome was mean change in BCVA between baseline and 2y. Secondary outcome variables included proportion of patients with a clinically significant change in BCVA (defined as an increase or decrease of ≥15 ETDRS letters), mean change in CRT, number of anti-VEGF injections, number of visits assessing disease activity and number of visits with active disease.

Statistical Analysis The present study was designed to test non-inferiority between between aflibercept and bevacizumab switch groups regarding the mean change in BCVA at 2y. The non-inferiority limit for the difference in mean change in BCVA was set to 5 ETDRS letters. With an assumed standard deviation (SD) for changes in BCVA of 15 ETDRS letters, we calculated a sample size of 112 patients per group would provide a power of 80%. The Shapiro-Wilk test was used for testing data normality. Student's *t*-test was used to test differences in baseline BCVA, baseline CRT, anti-VEGF injections administered, number of visits assessing disease activity, number of visits with active disease, and change in CRT at 2y. Mann-Whitney *U* test was used for testing differences in age at baseline. The Chi-square test was used to test differences in duration of symptoms, prior cataract surgery, cataract surgery during follow-up, and distribution of patients with a clinically significant improvement or worsening of BCVA. Fischer's exact test was used to test differences in neovascular membrane type and location. The paired *t*-test was used for testing differences in BCVA and CRT between baseline and 2y. Means are presented with SD. The statistical analyses were done in SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., USA).

RESULTS

Baseline characteristics of the bevacizumab switch and aflibercept groups are shown in Table 1. There were no significant differences in age, BCVA, neovascular membrane type or localization, duration of symptoms or cataract surgery prior to nAMD treatment between the study and the control groups at baseline.

There was no statistically significant difference in BCVA in the bevacizumab switch group (61.0 *vs* 62.1 ETDRS letters, *P*=0.463), nor in the aflibercept group (63.5 *vs* 65.3 ETDRS letters, *P*=0.137) between baseline and 2y.

The mean difference in BCVA between baseline and 2y was 1.13±14.47 ETDRS letters in the bevacizumab switch group, and 1.81±13.01 ETDRS letters in the aflibercept group (Figure 3). The lower bound of the 95% confidence interval of the difference in BCVA was -4.25, indicating non-inferiority within a 5 ETDRS letter limit.

No difference in distribution of patients with a clinically significant improvement (*P*=0.598), or worsening (*P*=0.508) of BCVA between baseline and 2y (Figure 4).

Figure 5 shows mean change in CRT from baseline to 2y. Mean CRT decreased substantially in both groups, bevacizumab switch (430.4±164.5 to 244.6±108.0 μm, *P*<0.001) and aflibercept groups (446.5±168.8 to 297.1±140.9 μm, *P*<0.001). There was no significant difference in mean change of CRT between baseline and 2y (study -185.9±167.0 *vs* control -149.4±193.1 μm, *P*=0.127). Our study was not sufficently powered for assessing non-inferiority of the mean difference in CRT, assuming an SD of a 100 μm.

There was no statistically significant difference in the distribution of patients having cataract surgery during follow-up (6 *vs* 10 controls, *P*=0.317).

There was no statistically significant difference in the number of anti-VEGF injections administered (12.76±2.20 *vs* 13.10±4.20, *P*=0.442), number of visits assessing disease activity with OCT (10.07±1.98 *vs* 10.49±3.88, *P*=0.301), or number of control visits with active disease (2.51±2.33 *vs* 3.17±3.02, *P*=0.065) in the study versus aflibercept groups respectively.

DISCUSSION

In this study, we found a TER switching to bevacizumab to be non-inferior to continued aflibercept treatment in nAMD with regards to change in visual acuity at 2y.

In addition, there were no statistically significant differences between the groups in mean change of CRT, the proportion of patients with a change in BCVA of ≥15 ETDRS letters, the number of anti-VEGF injections administered, the number of visits assessing disease activity, or the number of visits with active disease.

Although there are a large number of studies investigating the effect of changing from bevacizumab to ranibizumab or

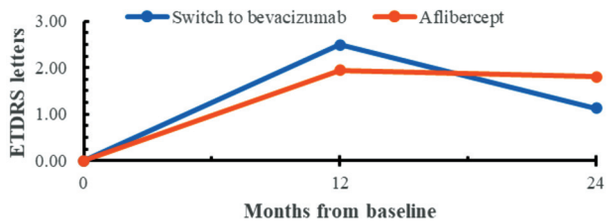

Figure 3 Mean change in BCVA from baseline BCVA: Best corrected visual accuity; ETDRS: Early Treatment Diabetic Retinopathy Study.

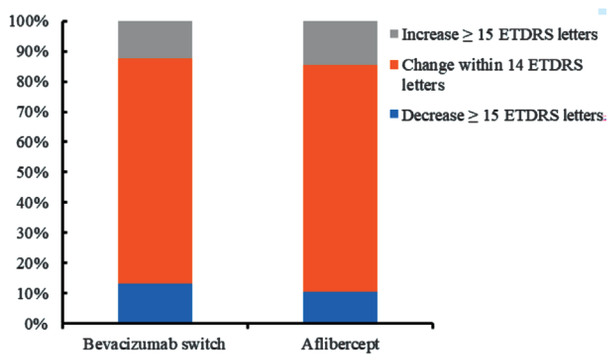

Figure 4 Change in BCVA between baseline and 2y, percentage of subjects in study and control groups respectively BCVA: Best corrected visual accuity; ETDRS: Early Treatment Diabetic Retinopathy Study.

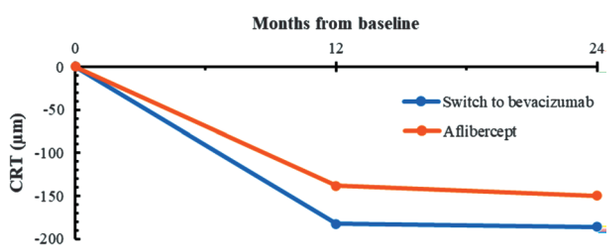

Figure 5 Mean change in CRT from baseline CRT: Central retinal thickness; ETDRS: Early Treatment Diabetic Retinopathy Study.

Table 1 Baseline characteristics mean±SD

Baseline characteristics	Bevacizumab switch	Aflibercept	*P*
Age (y)	79.7±6.7	77.1±6.9	0.076
BCVA baseline (ETDRS letters)	61.0±11.4	63.5±12.0	0.106
Central retinal thickness (μm)	430.4±164.5	446.5±168.8	0.466
Neovascular membrane type, *n*			0.747
Occult	43	40	
RAP	16	22	
PCV	4	2	
Non gradable	21	24	
Classic	30	28	
Localization neovascular membrane, *n*			0.200
Not graded	23	32	
Subfoveal	69	58	
Juxtafoveal	18	23	
Extrafoveal	4	1	
Duration of symptoms, *n*			0.341
<2mo	52	62	
2-4mo	30	30	
4-6mo	11	12	
>6mo	21	12	
Prior cataract sugery, *n*			0.352
No	79	73	
Yes	35	42	

SD: Standard deviation; BCVA: Best corrected visual accuity; ETDRS: Early Treatment Diabetic Retinopathy Study; RAP: Retinal angiomatous proliferation; PCV: Polypoidal choroidal vasculopathy.

aflibercept, we are not aware of studies assessing the effect of systematically changing from aflibercept to bevacizumab. Two smaller studies have retrospectively analyzed patients switching from either aflibercept or ranibizumab to bevacizumab. Waizel *et al*[20] studied 19 eyes receiving bevacizumab after intial treatment with 6.5±2.8 aflibercept injections. The eyes received a total of 5.4±3.2 injections of bevacizumab and were followed for 58.9±27.0 (range 16-112)wk. There were no statistically significant differences in BCVA and central macular thickness during aflibercept and bevacizumab treatment. Yamada *et al*[21] analyzed 7 eyes showing no difference in BCVA and a statistically significant reduction in foveal retinal thickness, 6mo after switching from ranibizumab to bevacizumab. Although methodologically different from our current study, the results from these publications are in line with our findings.

Our results suggest that switching to off-label bevacizumab in patients responsive to aflibercept yields similar results with regard to visual acuity. The protocol described in the study could offer a method of selecting patients more likely to respond to bevacizumab treatment, and might be a viable option in clinical settings with limited resources. Switching to bevacizumab may be a cost-effective treatment in selected patients responding well to aflibercept therapy. Aging populations worldwide are likely to increase the demand for medical retina services in the future, and highlight the importance of finding cost-effective treatments for nAMD.

The strengths of our study compared to previous studies are the use of high-quality data from the Swedish Macular Register, the presence of a control group, a larger sample size, and a longer follow-up time.

Human and animal studies have indicated a longer vitreous half-life of aflibercept compared to bevacizumab[23]. In the TER protocol used in our study subjects, the switch of drugs in the study group was done after a prolongation of the treatment interval to 8wk. Assessing whether reactivations are due to an inadequate response to bevacizumab, or shorter time of action is therefore not possible within the scope of this study. In our material, the longer half-life of aflibercept did not manifest as a higher number of visits with active disease or anti-VEGF injections administered.

There are several limitations to our study. Since historical patients were required for a comparable control group the risk of selection bias is introduced. All participants in our study belonged to a selected group responding well to both aflibercept treatment and the extension of treatment interval, which should be considered when interpreting our results. Although all subjects were treated in the same clinical setting, our data is not controlled for several factors that might vary over time. The demand for medical retina services and waiting times for treatment, change in staff, routines for entering data into the SMR, and technological advancements are examples of factors that might have a bearing on our results. As patients with severe adverse events were unlikely to complete the 2y follow-up, the risk of survivorship bias should be considered. Assuming similar safety profiles for bevacizumab and aflibercept, the likelyhood of bias is low. Although the follow-up time in our study is longer than other comparable studies, we lack long-term data on the efficacy and safety of the treatment protocols studied. Both the study and control groups consisted almost exclusively of Caucasians, and the results may not be applicable to other or more heterogenous populations.

Future research should aim to understand which patients would be best suited for switching to a more cost-effective anti-VEGF agent. Larger prospective studies are needed to elucidate the potential role of swithching anti-VEGF agents in an efficent, safe and cost-effective therapeutical approach to nAMD.

In conclusion, switching from aflibercept to bevacizumab was found to be non-inferior compared to continued aflibercept treatment, with regard to change in visual acuity at 2y.

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Conflicts of Interest: Kananen F, None.

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