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Switch of anti-VEGF agents is an option for nonresponders in the treatment of AMD

C Ehlken, S Jungmann, D Böhringer, HT Agostini, B Junker and A Pielen

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Evaluate primary therapy of exudative AMD.
2. Assess the efficacy of switching anti-VEGF treatments among nonresponders with AMD.
3. Distinguish the most important variable associated with the efficacy of switching anti-VEGF treatments among nonresponders with AMD.
4. Identify an effective treatment strategy that may improve visual acuity among anti-VEGF nonresponders with AMD.

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CLINICAL STUDY

Switch of anti-VEGF agents is an option for nonresponders in the treatment of AMD

C Ehlken[1], S Jungmann[1], D Böhringer[1], HT Agostini[1], B Junker[1,2] and A Pielen[1,2]

Abstract

Background **Although anti-VEGF therapy of exudative AMD with bevacizumab and ranibizumab proved efficacious in the majority of patients, CNV activity does not respond to continued treatment after repeated injections in a considerable amount of patients. These are referred to as nonresponders. A change of the drug to bevacizumab or ranibizumab could possibly offer an alternative option for the treatment of nonresponding exudative AMD.**

Methods and materials **A total of 138 nonresponders who switched therapy from bevacizumab to ranibizumab ($n = 114$) or vice versa ($n = 24$) were included in a retrospective study. Visual acuity (VA) and foveal thickness before and after the switch of therapy were compared. By means of linear regression analysis, we analyzed possible prognostic factors associated with a favorable outcome for visual acuity.**

Results **Linear regression analysis revealed a statistically significant benefit for nonresponders when treatment was changed to a different anti-VEGF drug (bevacizumab or ranibizumab). VA at the time of the switch was positively correlated with a beneficial development of VA after changing the drug. There was no significant correlation with age, macular thickness, number of injections before the switch, or the development of VA under treatment before the switch. Both patients switching to Avastin and Lucentis benefitted without statistically significant differences.**

Conclusions **An exchange of bevacizumab with ranibizumab or vice versa should be considered in nonresponders in the treatment of exudative AMD. Further prognostic factors may help to identify patients who might benefit from a switch. These factors should be investigated in further studies.**

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Introduction

Intravitreal injections of anti-VEGF agents are now the standard in the treatment of exudative age-related macular degeneration (AMD).[1] Pegaptanib, an aptamer targeting VEGF-A165, was first approved for the treatment of AMD.[2] It has been succeeded by two drugs that have been more efficacious: the humanized IgG antibody bevacizumab (Avastin), and ranibizumab (Lucentis), containing only the antigen-binding part of the antibody. Although ranibizumab was presumed to have a better effect, on the basis of a higher affinity to the target VEGF,[3] two large head-to-head-studies demonstrated a comparable efficacy of the two drugs in the treatment of exudative AMD.[4–6] Recently, a third drug, aflibercept, has been approved for the treatment of exudative AMD and poses a new therapeutic option.

However, still up to one-fourth of all treated patients do not benefit from intravitreal injections and visual acuity (VA) deteriorates even under treatment. This group has been described as nonresponders. Definitions for nonresponders vary, ranging from morphologic definitions (eg, remaining intra- or subretinal fluid (IRF or SRF) under treatment) to functional outcomes (eg, deterioration of best corrected visual acuity (BCVA) or even a stable BCVA without improvement) or combinations of both. Up to now, there is no consensus, whether and how nonresponders should be treated. Combinations with other treatment forms have been discussed, for example, combination with photodynamic therapy (PDT) or brachytherapy.

[1]Eye Center, Albert-Ludwigs-University, Freiburg, Germany

[2]Hannover Medical School, Hannover, Germany

Correspondence:
C Ehlken, Eye Center, Albert-Ludwigs-University, Killianstrasse 5, Freiburg 79106, Germany.
Tel: +49 761 270 40010;
Fax: +49 761 270 40630.
E-mail: christoph.ehlken@uniklinik-freiburg.de

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However, results have not been encouraging in patients with chronic AMD and there is currently no rationale to widely use these combinations in nonresponders.[7–10] Increasing the dose of ranibizumab was efficacious in some patients.[11]

After the FDA approval of ranibizumab, several groups reported about a switch from bevacizumab to ranibizumab[12,13] and found a comparable effect after the switch, though not only nonresponders were included. Two groups demonstrated a beneficial effect for patients with chronic AMD, switching from ranibizumab to bevacizumab[14] and from ranibizumab to aflibercept.[15]

In our retrospective study, we investigated the outcomes of patients identified as nonresponders switching from ranibizumab to bevacizumab or vice versa. We analyzed if the patients benefitted from the switch and evaluated prognostic factors that were supposed to help in identifying patients who might benefit from a change of the drug.

Materials and methods

Study design

The retrospective study was approved by the local ethics committee of the University of Freiburg, Germany. We obtained written informed consent on the anonymous analysis of clinical data in all patients. The study adhered to the Declaration of Helsinki.

The purpose of the study was to evaluate if patients who did not improve under therapy (nonresponders) with an anti-VEGF (bevacizumab or ranibizumab) agent improved after switching to the other drug, and if factors could be identified, which help to identify patients who might benefit from a switch.

Screening

All patients treated with bevacizumab and ranibizumab at the University Eye Hospital, Freiburg, were identified by a database search for the terms 'bevacizumab' and 'ranibizumab'. These subjects were entered into a database. Inclusion and exclusion criteria were checked for the identified subjects.

Inclusion criteria: patients who have been treated for exudative AMD with at least three consecutive monthly intravitreal injections with an anti-VEGF agent (bevacizumab or ranibizumab) and were unresponsive to treatment (no improvement or deterioration in visual acuity and morphology, ie, stable or increasing sub- or intraretinal fluid (SRF or IRF) as assessed by OCT). Patients switched to three monthly injections of the other agent with the first injection within 100 days after the last injection of the first agent. Exclusion criteria: indication other than AMD, other reasons for deterioration of BCVA (eg, change of lens status during the time of the study, uncontrolled glaucoma), any pre-treatment with intravitreal injections other than anti-VEGF, photodynamic therapy (PDT), or macular surgery, macular hemorrhage involving the fovea during the study, intraocular surgery during the course of the study (eg, cataract surgery). If both eyes fulfilled the inclusion criteria, only the eye that first received treatment was included.

Statistical analysis

We reviewed the medical records and collected data on BCVA and macular thickness from OCT measurements. We entered all intravitreal injections into the database. We assessed the date when bevacizumab was exchanged by ranibizumab or vice versa. The change of visual acuity in EDTRS lines that occurred before and after the switch of treatment was calculated. Central retinal thickness was determined over time. OCT measurements were performed with both the Stratus (Carl Zeiss Meditec, Oberkochen, Germany) and Spectralis (Heidelberg Engineering, Heidelberg, Germany) tomographers.

We compared BCVA in EDTRS lines before and after switch with the paired *t*-test for each group separately. Change in central retinal thickness was assessed accordingly.

We assessed by means of multiple linear regression analysis, whether age, current treatment (bevacizumab *vs* ranibizumab), logBCVA before treatment switch or central retinal thickness from the OCT are predictive for a gain in EDTRS lines after a treatment switch. The linear model was additionally adjusted for the OCT device (Stratus *vs* Spectralis).

Results

Search Results

In the screening, 435 patients were identified. Of those, 138 fulfilled the inclusion criteria, 114 in group 1 (switch from bevacizumab to ranibizumab) and 24 in group 2 (switch from ranibizumab to bevacizumab). Main reasons for exclusion were unsuitable therapy regimen (eg, more than 100 days between switch of anti-VEGF agent, or less than three monthly intravitreal treatments before or after switch), other additional underlying pathologies of the macula (eg, diabetic macular edema, macular pucker), ocular surgery during the time of switch (eg, cataract surgery), pre-treatment with PDT, triamcinolone, or Macugen, or macular hemorrhage in the fovea. VA and OCT data were available for 124 and 107 patients, respectively, in group 1 and all patients in group 2.

Table 1 Group characteristics

	Group 1 (bevacizumab to ranibizumab)	*Group 2 (ranibizumab to bevacizumab)*	P-*value*
Number of subjects	114	24	
Women	77 (68%)	17 (71%)	0.753
Age (years)	77.8 ± 8.2	77.5 ± 7.5	0.675
Visual acuity, time of switch (logMAR)	0.52 ± 0.3	0.41 ± 0.3	0.049
Macular thickness, time of switch (μm)	418 ± 166	340 ± 131	0.037
Number of injections before switch	9.8 ± 4.6	8.9 ± 4.0	0.316
Better eye treated	53 (46%)	9 (38%)	0.421

The characteristics for both groups are displayed in Table 1. The groups differed significantly in VA and macular thickness in OCT at the time of the switch of medication ($P<0.05$). However, all other investigated parameters were similar in both groups.

Visual Acuity and macular thickness

The gain/loss in ETDRS lines before and after the switch for both groups is shown in Figure 1. In group 1, while VA decreases slightly under treatment with bevacizumab, visual acuity improves significantly after the switch to ranibizumab ($P<0.001$). In group 2, VA decreases slightly under therapy with ranibizumab, and does not improve statistically significantly after switching from ranibizumab to bevacizumab ($P=0.52$).

The change of macular thickness before and after the switch is displayed in Figure 2. In group 1, macular thickness decreases significantly after switching from bevacizumab to ranibizumab by a mean of 66 μm ($P<0.001$). In group 2, there is no statistical difference of macular thickness during the course of the therapy (mean change of 28 μm, $P=0.67$).

Figure 3 shows the results for visual acuity and macular thickness, when both groups are combined.

Linear Regression Analysis of prognostic factors

Results of the multiple linear regression analysis of prognostic factors are shown in Table 2. Of the included parameters, the VA at the time of switching the anti-VEGF therapy was statistically significantly positively correlated with the VA after the switch. A higher VA before switch was associated with a better outcome for the patient. Gain or loss of letters before the switch was not correlated with the outcome after the switch.

We did not observe a statistically significant association with the group (switch from bevacizumab to ranibizumab or vice versa) and the VA. Our model

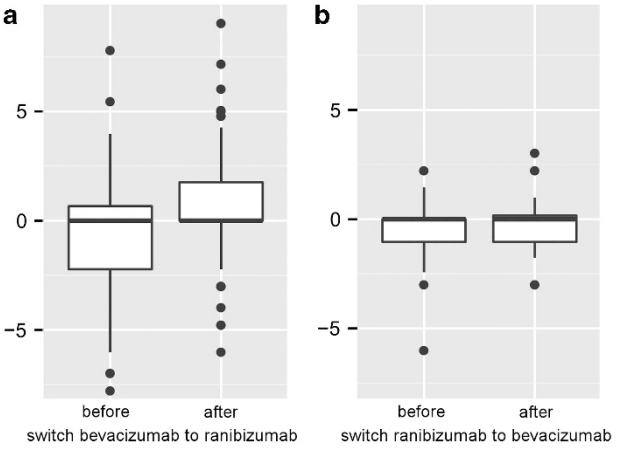

Figure 1 Visual acuity before and after switch of therapy, groups 1 and 2. Change of visual acuity in lines after three injections before (left) and after (right) the switch from bevacizumab to ranibizumab (a, 124 patients) and from ranibizumab to bevacizumab (b, 24 patients).

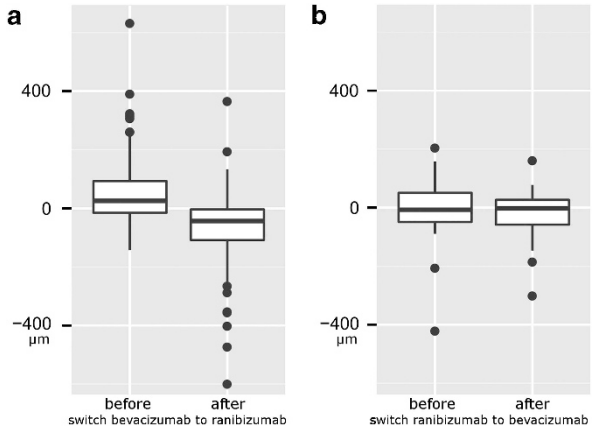

Figure 2 Macular thickness before and after switch of therapy, groups 1 and 2. Change of macular thickness as measured by OCT after three injections before (left) and after (right) the switch from bevacizumab to ranibizumab (a, 107 patients) and from ranibizumab to bevacizumab (b, 24 patients).

included the OCT manufacturer to control for a potential calibration bias. Macular thickness before the switch did not exert a statistically significant effect on VA.

Discussion

It is not known, yet, why some patients do not respond to anti-VEGF treatment or develop into nonresponders during the course of the treatment. Tachyphylaxis has been discussed to be important in the development of a resistance to intravitreal injections.[16,17] However, the mechanisms are not clear. In some cases, high doses of ranibizumab (2.0 mg opposed to the regularly used 0.5 mg) could yield a response in patients with persisting SRF or IRF under monthly injections of ranibizumab.[11]

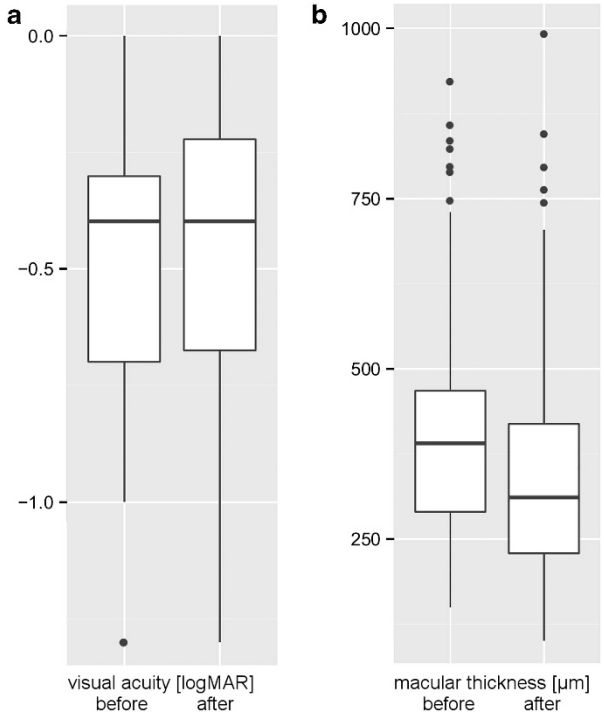

Figure 3 Visual acuity and macular thickness, groups combined. Visual acuity (a) and macular thickness (b) before and after switch of therapy for all patients.

Table 2 Linear regression analysis of prognostic factors

	Beta value	*Power*
Intercept	$+0.09 \pm 0.20$	0.65
Age (in years)	$+0.001 \pm 0.002$	0.64
Switch to bevacizumab/ranibizumab	$+0.03 \pm 0.05$	0.53
Visual acuity before switch (log10)	$+0.19 \pm 0.08$	0.02
Change of visual acuity before switch	-0.10 ± 0.10	0.30
Macular thickness before switch (in μm)	$< -0.001 \pm < 0.001$	0.14
Stratus/Spectralis OCT	-0.04 ± 0.05	0.38

Genetic variants of the VEGF gene[18] seem to alter the response to anti-VEGF treatment. Although both bevacizumab and ranibizumab bind VEGF, minor differences in the binding properties might explain a differential response to different anti-VEGF agents, and might offer the possibility of a response even in patients who developed a tolerance to one drug.

In our study, nonresponders to either bevacizumab or ranibizumab benefitted from a switch to the other drug. Linear regression analysis revealed that VA at the time of the switch of medication was the only prognostic factor (of the ones analyzed) for the development of VA. Patients with a better VA had a better chance of gaining further after the switch. It did not matter if the patients had been treated with bevacizumab or ranibizumab before. This seems to contradict the results from the analysis of the two treatment groups, where a switch to bevacizumab appears to be less likely to end in a benefit for the patient (gain of 0.3 lines after switch to bevacizumab versus gain of 1.3 lines after switch to ranibizumab). However, this contradiction can be explained by the stage of disease at the time of the switch, as patients in group 2 (switch to bevacizumab) had a significantly lower VA and thus, regarding the linear regression analysis, a reduced chance of gaining VA. In addition to the lower VA, central foveal thickness was lower in group 2. Although morphologic data, such as scarring, or presence of SRF or IRF, have not been analyzed separately, this might be explained by a higher rate of patients with already (partially) scarred or fibrotic CNV, resulting in a poorer prognosis.

Visual acuity at the time of switch was identified as a prognostic factor, meaning that a better VA at the time of switch was correlated with a better response after the switch. However, there was no specific threshold in VA indicating a benefit after a switch of treatment. Thus, it is difficult to derive recommendations on the basis of VA in clinical practice. Morphologic parameters and spectral domain OCT have taken the main role for the controlling and management of therapy in responders, and a 'zero tolerance for fluid' was proclaimed as target of the therapy.[4] However, persisting IRF or SRF under therapy is an attribute of nonresponders and does not help in the decision whether further treatment is advised.

As far as we are aware, this is the first study reporting a considerable (>100 patients) study size of patients estimated as nonresponders switching from bevacizumab to ranibizumab.

The study is limited by its retrospective design. As bevacizumab was available first, this results in a difference between the two study groups, with more patients in the group switching from bevacizumab to ranibizumab than vice versa. In addition, as discussed above, groups differed significantly in the parameters VA and foveal thickness at the time of switch.

Central foveal thickness (as measured by OCT) was the only morphologic parameter chosen for this study. For further studies, additional criteria, such as the presence of intra- or subretinal fluid, pigment epithelium detachment, or subretinal fibrosis, should be added to the analysis.

There are two retrospective studies which reported about the results of patients switching from bevacizumab to ranibizumab, when the latter became available.[12,13] Stepien *et al*[13] observed a similar response after switching to ranibizumab in 84 patients. Karagiannis *et al*[12] observed a transient decrease in VA and increase in macular thickness, interpreted as a transient 'instability' after switching to ranibizumab. Three of the included 34 patients developed a significant macular hemorrhage after switching to ranibizumab. However, both studies included patients not regarded as nonresponders, and

response after switching to ranibizumab was to be expected.

Almony *et al*[14] observed a beneficial effect of switching from ranibizumab to bevacizumab in 50 nonresponders. A failing response to ranibizumab was defined as no improvement in VA and no improvement in subretinal fluid in fluorescein angiography and OCT. After the switch, patients gained a mean of 0.3 lines, comparable with group 2 in our study, although results varied from a loss of two lines to a gain of four lines among the included patients.

Gasperini *et al*[16] reported on 26 nonresponders, defined as no improvement in sub- or intraretinal fluid, or pigment epithelium detachment. Eight of ten patients responded (ie, total or partial resolution of fluid in OCT) after switching to ranibizumab. Thirteen of sixteen eyes responded after switching from ranibizumab to bevacizumab.

Kumar *et al*[15] reported a significant improvement in visual and anatomical outcomes in 34 eyes with persistent subfoveal fluid formerly treated with ranibizumab after switching therapy to aflibercept.

None of the aforementioned studies evaluated prognostic factors for patients who might benefit from a switch of anti-VEGF drugs.

Clinical management of nonresponders to anti-VEGF therapy is challenging for the patient and the physician. Different options have been proposed in case of a failing response to treatment. However, there is still no common sense as to what would be the best option for the individual. In our study, a significant proportion of patients classified as nonresponders benefitted from a switch of the anti-VEGF drug (bevacizumab or ranibizumab). Thus, a switch of therapy to another anti-VEGF drug should be considered in nonresponders. Further morphologic criteria should be investigated in clinical trials to help to identify patients who might benefit from a switch of therapy.

Summary

What was known before

- The majority of patients with neovascular AMD profits from the use of intravitreal injections of VEGF inhibitors such as bevacizumab and ranibizumab.
- Up to 25% of patients does not respond (anymore) to intravitreal injections of VEGF inhibitors during the course of therapy.
- Therapeutical options are limited for nonresponders.

What this study adds

- In nonresponders to anti-VEGF treatment for neovascular AMD, switching from ranibizumab to bevacizumab or vice versa can be beneficial and should be considered as an option.

Conflict of interest

The authors declare no conflict of interest.

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1. You are seeing a 67-year-old woman for the initial treatment of exudative age-related macular degeneration (AMD) with reduced visual acuity. In general, what should you consider regarding the therapeutic approach to this patient?

- A Intravitreal injections with pegaptanib remain the standard of care
- B Bevacizumab is more efficacious than ranibizumab
- C Up to one quarter of patients fail to benefit from intravitreal anti-vascular endothelial growth factor (VEGF) therapy
- D Photodynamic therapy is now considered a first-line treatment option

2. This patient receives monthly treatment with intravitreal bevacizumab, but her condition fails to improve after 4 months. According to the results of the current study by Ehlken and colleagues, what is the next best step in her care?

- A Continue treatment with bevacizumab
- B Change to treatment with ranibizumab
- C Treat her with both bevacizumab and ranibizumab
- D Change her treatment to photodynamic therapy plus ranibizumab

3. As you consider changing treatment, what was the most important variable in predicting a worse response to a change in anti-VEGF therapy in the current study?

- A Worse visual acuity
- B Older age
- C Higher macular thickness
- D Switch from bevacizumab to ranibizumab specifically

4. In the current study, which of the following treatment strategies was effective in improving visual acuity among nonresponders to anti-VEGF therapy?

- A Changing treatment from bevacizumab to ranibizumab only
- B Changing treatment from ranibizumab to bevacizumab only
- C Changing from either bevacizumab or ranibizumab to the other anti-VEGF drug
- D No efficacy in switching anti-VEGF treatments

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organised clearly for learning to occur.

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice.

Strongly disagree				Strongly agree
1	2	3	4	5

4. The activity was presented objectively and free of commercial bias.

Strongly disagree				Strongly agree
1	2	3	4	5