

Aflibercept efficacy in refractory choroidal neovascularization

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Abstract

The aim of the report is to evaluate the short-term efficacy and safety of aflibercept (EYLEA®) in patients with choroidal neovascularization (CNV) transformed into refractory during treatment with bevacizumab (AVASTIN®).

Methods: Clinical, morphological, and functional changes were retrospectively evaluated in cases with refractory CNVs to monthly 1.25 mg bevacizumab intravitreal injections (AVASTIN®) and switched to 3 monthly 2.0 mg intravitreal injections of aflibercept (EYLEA®).

Results: In this pilot evaluation, 8 cases of CNVs that become refractory to intravitreal treatment with 1.25 mg intravitreal bevacizumab (AVASTIN®), were switched to 2.0 mg intravitreal aflibercept (EYLEA®) and evaluated. The mean age of patients was 67.6 years (54-74 years). In 7 cases, CNV was associated to age related macular degeneration and in 1 case to angioid streaks. The mean number of previous intravitreal bevacizumab (AVASTIN®) administrations was 9.32 (7-12). In all cases, the last 3 intravitreal injections of bevacizumab were performed at an interval of maximum 6 weeks. The refractory status was confirmed by the lack of improvement or worsening of the clinical features as revealed by SD-OCT. A slowly anatomical improvement was noticed in 5 out of 8 cases (62.5%) since the first aflibercept administration. The anatomical improvement was stable after 3 monthly administrations. During the treatment, only 3 out of 5 cases (60%) showing anatomical improvement had a minor visual benefit (one line of VA gain). In 3 cases, the treatment change was unremarkable. No side effects were noticed.

Conclusions: The anatomical improvement confirms previous reports regarding the efficacy and safety of aflibercept (EYLEA®) in some cases of CNV that became refractory during conventional anti-VEGF therapy. The improvement can be, at least partially, explained by the more complex features of aflibercept. Unfortunately, a minor visual benefit was noticed in a limited number of cases.

Keywords: Aflibercept, Refractory Choroidal Neovascularization

Introduction

Choroidal neovascularization (CNV) is a

common but severe complication encountered in several chorioretinal diseases, most frequent in age related macular degeneration (AMD) [1]. AMD is a leading cause of blindness in elderly

people [2]. The worldwide prevalence for both the early and the late onset AMD is greater than 8%, with an estimated number of 196 million people affected in 2020 [3].

The cornerstones of pathogenesis in CNVs are angiogenesis and inflammation, which will lead to the development of new blood vessels capable of proliferation and invasion of both the retinal pigment epithelium (RPE) and the outer retina [1].

The proliferative angiogenic response, resulting in the development of CNV in the wet form of AMD, has a complex pathogenesis. The immune system, the complement pathway and inflammation are all involved, leading to RPE damage, blood-retinal barrier breakdown, and accumulation of immune cell infiltration that will stimulate the proliferative angiogenic response and the vascular endothelial growth factor (VEGF) synthesis. Therefore, an abnormal vascular network associated with fluid leakage will result [4].

The current standard of care in CNVs has shifted in the latest years from laser treatment and/or photodynamic therapy towards a more targeted blocking of vascular proliferation, thus limiting the further extension of the lesions and stopping the leakage. One of the most potent proliferative factors is the VEGF family with its isoforms. Therefore, there is a series of immune therapies aimed at suppressing this factor. Bevacizumab is a full-length recombinant monoclonal specific antibody that targets all isoforms of VEGF-A [5]. Ranibizumab is a smaller monoclonal antibody, derivative from bevacizumab and with a similar mechanism of action as bevacizumab, approved since 2007 in both USA and Europe for treatment of CNVs secondary to AMD. Due to the affordable price, favorable safety profile, and comparable efficacy, bevacizumab is still widely used as an off label treatment of macular diseases that involve subretinal neovascularization [1].

Some patients with CNVs are either primary non-responders or become refractory in time to bevacizumab therapy. Lux et al. found that 45% of the patients with CNVs due to AMD were non-responders to conventional therapy, and the predictor of treatment failure was the extent of lesions, significantly larger in the non-responders group [6]. A possible explanation for the decreasing response to treatment in time can be related to monthly bevacizumab administration.

This might decrease the bioefficacy of the drug, phenomenon known as tachyphylaxis [7].

As increasing the dose or reducing the interval between administrations failed to overcome tachyphylaxis, one of the newest strategies in refractory CNV is to switch to another anti-VEGF drug [8,9].

Bakall et al. reported the potential beneficial impact of aflibercept in AMD patients with CNVs refractory to bevacizumab or ranibizumab [10]. Aflibercept is the newest approved anti-VEGF drug, a powerful recombinant fusion protein that binds to all isoforms of VEGF-A, VEGF-B, and placenta growth factor (PGF). Aflibercept has the highest affinity for VEGF-A as compared to all other anti-VEGF [11] and proved higher anatomic efficacy than bevacizumab or ranibizumab [12]. Apart from inhibiting angiogenesis, anti VEGF drugs reduce vascular leakage and edema leading to subsequent reduction of the macular thickness [13].

The aim of this report was to evaluate the short-term morphological and functional changes when bevacizumab was switched to aflibercept in cases transformed into refractory CNVs.

Material and Methods

A series of 8 cases with refractory CNVs during treatment with 1.25 mg intravitreal bevacizumab were switched to 3 monthly injections of 2.0 mg aflibercept, in order to evaluate the efficacy and safety of aflibercept as a "rescue" therapy in refractory CNVs. The CNVs were associated with neovascular AMD in 7 out of 8 cases, and to angioid streaks in 1 case. All cases benefited from a complete monthly ophthalmic evaluation, including best-corrected visual acuity (BCVA) and spectral domain optical coherence tomography (SD-OCT).

Most of the patients included in this case series were old, with a mean age of 67.6 years (54-74 years). Each patient was initially successfully treated with repeated doses of 1.25 mg bevacizumab, the mean number of intravitreal administrations of bevacizumab before switching to aflibercept was 9.32 (7-12). In all cases, the last 3 intravitreal injections of bevacizumab, performed at a maximum 6 weeks interval, were ineffective proving the refractory status of CNVs. The lack of improvement or even worsening of

the clinical features was also documented by the SD-OCT evaluation.

Results

A total of 5 out of 8 cases (62.5%) showed an anatomical improvement after switching to 2.0mg aflibercept intravitreal injection. The anatomical recovery paralleled all the 3 monthly administrations. In particular, SD-OCT proved as main monitoring tool, providing the finest evaluation of RPE configuration and subretinal fluid and intraretinal abnormalities evolution [14,15]. A brief description of these cases is presented below, along with the OCT scans.

Case 1

A 65-year-old male patient who successfully underwent 6 previous administrations of 1.25 mg bevacizumab for subfoveal CNV due to neovascular AMD, showed worsening of both BCVA and clinical aspect during the last 3 injections with persistent subretinal fluid (Fig. 1).

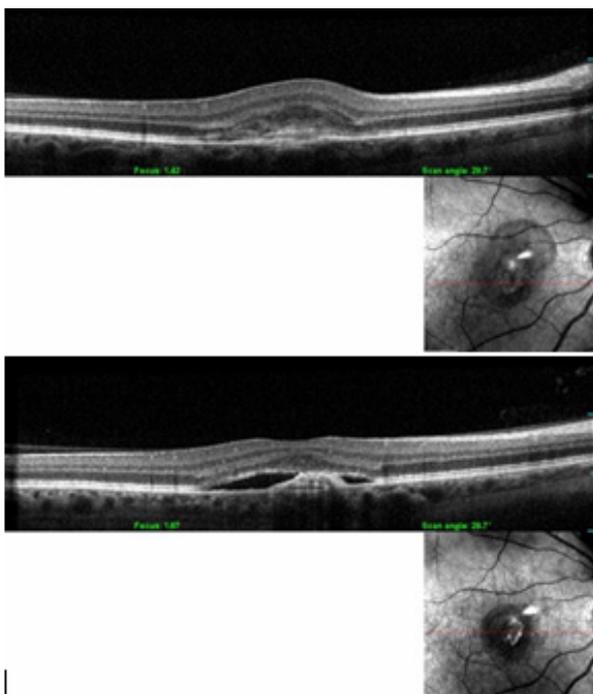


Fig. 1 Case 1: Worsening of anatomical condition during the last 3 bevacizumab injections

After the first injection of aflibercept, a mild anatomical improvement was noticed, which continued throughout the treatment (Fig. 2). The

anatomical improvement was not paralleled by the BCVA improvement.



Fig. 2 Case 1 after the 1st and 3rd aflibercept injection – continuous reducing in both RPE elevation and subretinal fluid but no visual gain

Case 2

A 73-year-old male patient with neovascular AMD, received a total of 6 injections of intravitreal bevacizumab, with a lack of improvement during the last 3 injections (Fig. 3).

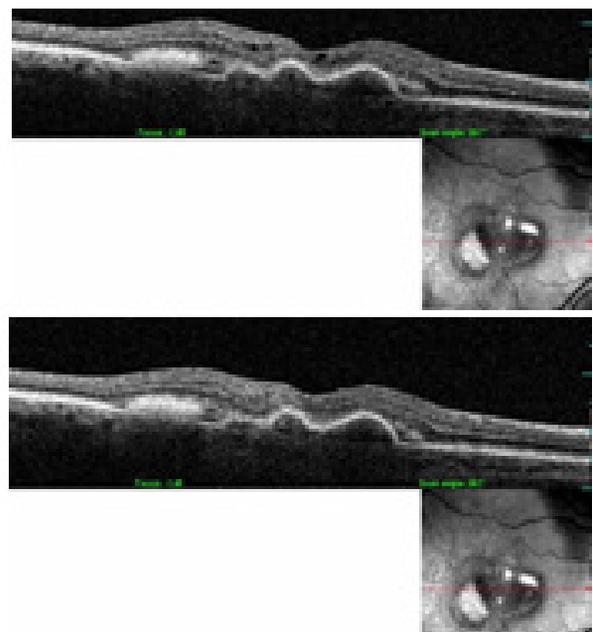


Fig. 3 Case 2: no anatomical improvement during last 3 injections of bevacizumab

After switching to aflibercept, the anatomical aspect significantly improved immediately after the first injection. After the 3rd injection of aflibercept, the PED disappeared but a large intraretinal degenerative cyst was still present (Fig. 4). No BCVA improvement was noticed.

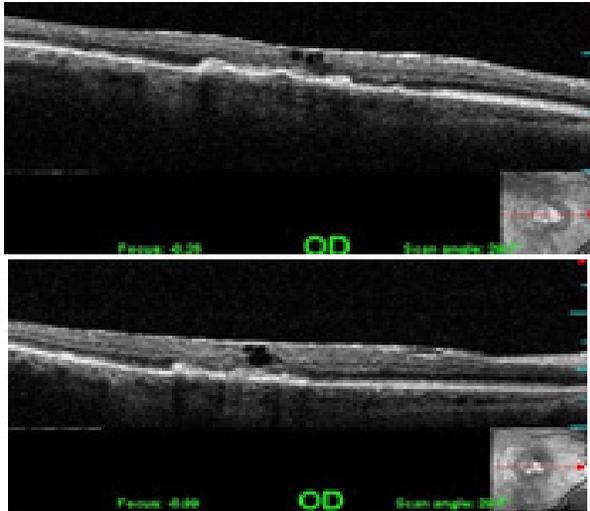


Fig. 4 Case 2: anatomical improvement after the 1st and 3rd aflibercept injections: PED disappearance but intraretinal degenerative cyst persistence

Case 3

A 54-year-old male patient received a total of 5 bevacizumab injections for juxtafoveal CNV due to angioid streaks. During last 3 administrations of bevacizumab, the OCT examination showed a further thickening of the macula and increase of the cystoid spaces (Fig. 5).

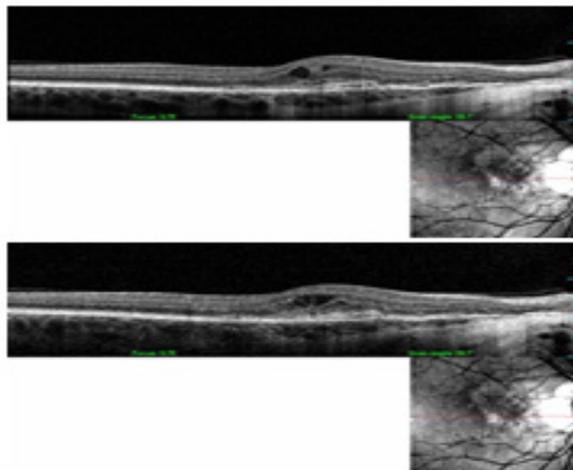


Fig. 5 Case 3: CNV due to angioid streaks worsening during the last 3 intravitreal bevacizumab administrations

The aflibercept therapy in this case greatly improved both the macular architecture and the BCVA. The OCT cross section after the 3rd aflibercept injection revealed the disappearance of cystoid spaces and the reduction of macular thickness (Fig. 6).

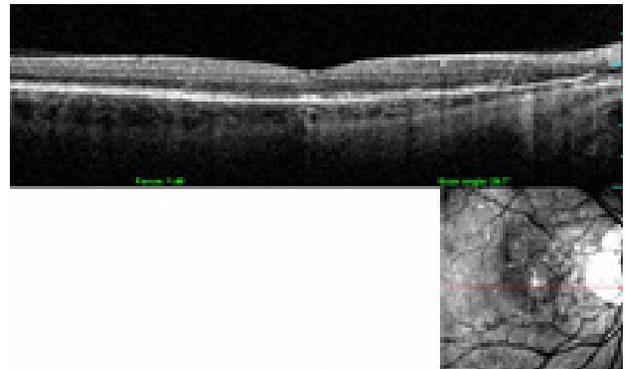
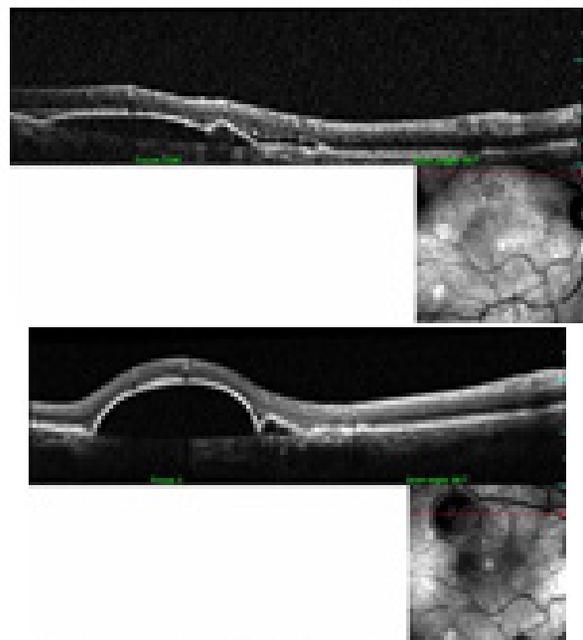


Fig. 6 Case 3: improved macular scan after 3 aflibercept injections

Case 4

A 69-year-old female patient underwent 9 previous bevacizumab intravitreal injections for CNV, due to neovascular AMD. After a significant clinical improvement, a large new unresponsive PED developed despite the additional treatment (Fig. 7).



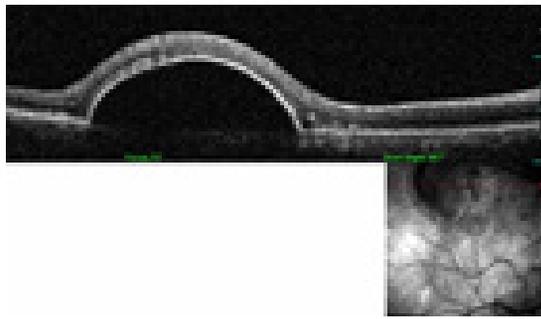


Fig. 7 Case 4: The OCT scans and the SLO fundus images show a significant worsening of the macular lesions despite the 3 monthly bevacizumab intravitreal injections

After switching to aflibercept, a slow progressive anatomical improvement was noticed in both reduction of PED height and extension (Fig. 8). Unfortunately, only a mild improvement in BCVA was noticed.

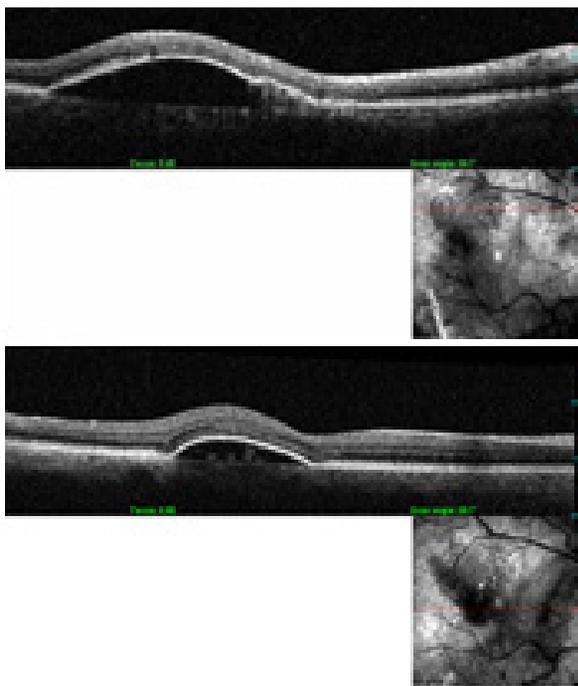


Fig. 8 Case 4: progressive PED reduction after the 1st and 3rd aflibercept injections

Case 5

This case was somehow particular because of the patients' outstanding improvement after switching the anti-VEGF therapy from bevacizumab to aflibercept. The 71-year-old male patient, with a large area of serous retinal detachment due to neovascular AMD, proved quickly unresponsive after 2 intravitreal injections of 1.25mg bevacizumab. A total

remission of subretinal fluid was obtained with only 2 intravitreal injections of 2mg aflibercept (Fig. 9). A mild improvement in BCVA was also noticed.

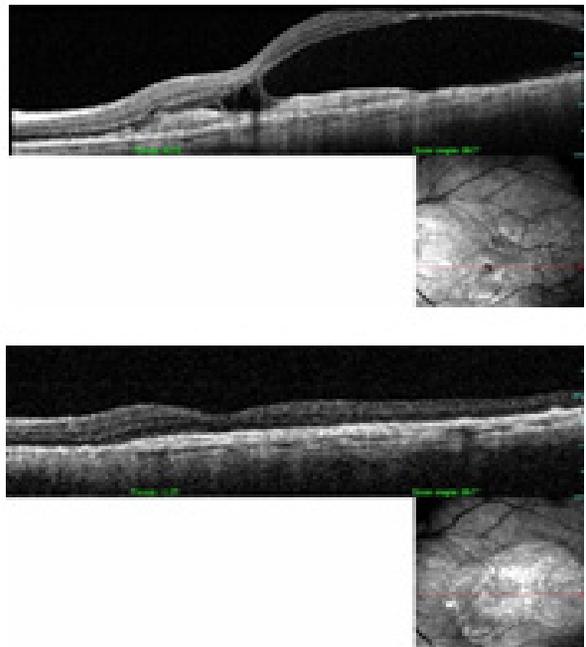


Fig. 9 Case 5: Total remission of subretinal fluid after 2 aflibercept intravitreal injections

Discussions

The retrospective analysis of our 8 cases with CNVs refractory to 1.25 mg intravitreal bevacizumab switched to 2.0 mg intravitreal aflibercept revealed that 5 out of 6 cases (62.5%) had a clinical and anatomical improvement confirmed by the SD-OCT findings. The other 3 cases rather showed a clinical stabilization during the aflibercept treatment with no additional BCVA loss.

Only 3 out of 5 improved cases (60%) also had a visual benefit, recovering a mean of one line of visual acuity. The other 2 patients might still have a chance for visual improvement in time, as BCVA does not always immediately parallel anatomical amelioration. On the other hand, Wickremasinghe et al. stressed that during the anti-VEGF therapy, BCVA could decrease in the absence of fluid on the OCT scans. However, when present, intra-retinal fluid is associated with poorer visual acuity [16].

Many studies have already suggested the positive effect of aflibercept therapy in patients

with neovascular AMD and CNVs resistant to either bevacizumab or ranibizumab [10,11,17-22].

In a retrospective analysis recently published in *Retina*, Kumar et al. reported that eyes with neovascular AMD resistant to intravitreal ranibizumab or bevacizumab improved under intravitreal aflibercept therapy. The anatomical improvement was confirmed by the reduction of subretinal fluid, intraretinal fluid, and subfoveal PED on OCT images. However, as it was also noticed in our series, regarding the visual function, Kumar et al. pointed out that there was no significant improvement of BCVA after 3 consecutive aflibercept administrations, and that after additional aflibercept injections there was a statistical significant but minor visual improvement [17].

In such cases of refractory CNVs, most authors agreed that the visual acuity rather stabilizes and rarely improves [17-22].

Hsia et al. recently reported that in a smaller number of cases, an anatomical improvement in all 5 refractory cases switched to aflibercept, and an increase of BCVA in 4 out of 5 eyes [11]. Of course, these results are limited to a small number of cases.

Aflibercept intravitreal injections were well tolerated. In our study, no ocular or systemic complications were noted during and after the intravitreal injection of standard dosage.

The limitations of this study are related to the retrospective design but mostly to the small number of cases evaluated. As already suggested, the OCT proved as a quick non-invasive, safe, and very effective tool to monitor the response to anti-VEGF intravitreal therapy [23].

Conclusions

The data collected from the presented case series suggest that most of the patients with refractory CNV to intravitreal bevacizumab may benefit from the therapeutic change to intravitreal aflibercept. Unfortunately, the anatomical improvement, spectacular in at least 2 of our cases, was not always paralleled by a significant increase in BCVA.

In our experience, aflibercept proved to be an effective rescue therapy in such cases, with good efficacy and safety. These results can be, at least partially, explained by the more complex bio-chemical interactions of aflibercept.

A larger number of patients and further

studies are necessary to assess this new therapeutic indication, the long-term efficacy and safety in such cases.

Disclosure

The authors decline any financial interest from this article.

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