Short-term morpho-functional changes in previously treated neovascular AMD eyes switched to brolucizumab

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Article

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Abstract

**Purpose:** To explore the morpho-functional fluctuations in eyes treated for nAMD when switched from aflibercept or ranibizumab to brolucizumab.

**Methods:** 31 eyes of 31 patients with nAMD with type 1 MNV were included. All patients were imaged using the SD-OCT. The OCT acquisition was performed at the following visits: (I) 1 month before the intravitreal injection of aflibercept or ranibizumab (T1), (I) 1 month after T1 and at the time of switch to brolucizumab injection (T2), and 1 month after the latter procedure (T3). The main outcome measures were: (1) Central macular thickness (CMT), (2) choroidal vascularity index (CVI) and, (3) subfoveal choroidal thickness (CT).

**Results:** CMT analysis showed fluctuations at 3 times. In detail, T2 displayed a thicker CMT in comparison to T1, although not statistically significant (p = 0.12). Contrariwise, T3 showed a thinner CMT in comparison to T2 (p = 0.002). Analyzing CVI among the three different times, the LCA and TCA showed significantly different values before and after switching to brolucizumab. T2 showed a significant reduction in both vessel lumen and total area compared to T1 (p = 0.032 and p = 0.046, respectively). Moreover, T3 showed a greater value of both LCA and TCA in comparison to T2 (p = 0.008 and p = 0.01, respectively). CT did not show significant differences at each time (P>0.05).

**Conclusions:** Our results reported early experiences on morpho-functional fluctuations in patients with nAMD switched to brolucizumab. The anatomical impact of brolucizumab administration appears to result in more effective resolution of SRF and IRF, in association with choroidal vascular swelling.

Summary Statement

We reported early experiences on morpho-functional fluctuations in eyes treated for neovascular age-related macular degeneration (nAMD) when switched from aflibercept or ranibizumab to brolucizumab.

Introduction

Neovascular age-related macular degeneration (AMD) is the primary cause of acquired irreversible vision loss in people aged more than 55 years in the Western world.\(^1\,^2\) Treatment of neovascular AMD is aimed at reducing exudation caused by macular neovascularization (MNV).\(^3\,^4\) Until recently, numerous therapeutic approaches have attempted demonstrating partial effectiveness.\(^5\,^6\) In the last decade, the introduction of intravitreal injections of anti-vascular endothelial growth factor (VEGF) molecules has allowed to expand the repertoire of treatments for neovascular AMD becoming the first-line therapy. The main anti-VEGF drugs include aflibercept (Eylea; Regeneron, Tarrytown, NY, USA and Bayer HealthCare, Berlin, Germany)\(^4\) and ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA).\(^8\) Importantly, frequent injections are needed to avoid inadequate efficacy.\(^9\,^10\)
The introduction of brolucizumab (Beovu; Novartis, East Hanover, NJ, USA) increased the number of therapeutic choices.\textsuperscript{11} In detail, brolucizumab is an antibody fragment that inhibits the VEGF-A isoform. This molecule is characterized by a smaller structure (26 KDa), this allowing an increased concentration of the drug within the retina and improved stability.\textsuperscript{12} Trials data (HAWK and HARRIER) have demonstrated that brolucizumab every 3 months is non inferior to fixed-dose aflibercept with respect to the change in best-corrected visual acuity (BCVA) from baseline to week 48. Moreover, the brolucizumab treatment seemed to be more efficacious in maintaining resolution of MNV activity markers including intraretinal fluid (IRF) or subretinal fluid (SRF).\textsuperscript{11,12}

Structural optical coherence tomography (OCT) has provided the capability to provide metrics reflecting the retinal and choroidal anatomy (e.g central retinal thickness\textsuperscript{13} choroidal vascular index\textsuperscript{14} or subfoveal choroidal thickness\textsuperscript{15}). Accordingly, structural OCT has been employed to observe and quantify the effect of intravitreal anti-VEGF therapy in neovascular AMD. In particular, previous reports described choroidal and retinal changes occurring after ranibizumab or aflibercept therapies and demonstrated significative differences in terms of morpho-functional modifications between these two molecules.\textsuperscript{16,17} The characterization of these morpho-functional biomarkers during anti-VEGF therapy may be important for the optimal management of neovascular AMD and for a better comprehension of the different treatments. Considering this, it would be important to characterize the impact of intravitreal injections of brolucizumab on these morpho-functional parameters reflecting the choroidal and retinal structure.

In the current study, using structural OCT, we evaluated the morpho-functional changes in eyes treated for neovascular AMD when switched from aflibercept or ranibizumab to brolucizumab. This could identify helpful biomarkers for disease management.

**Results**

**Characteristics of subjects included in the analysis**

A total of 31 eyes of 31 Caucasian patients with neovascular AMD were included in the study. Eighteen patients were females and 13 patients were males. The mean age was 72.5 ± 7.5 years (range 52–85 years). The switched patients had received an average of 10.2 ± 8.34 (range 3–22 years) of intravitreal injections of anti-VEGF drugs prior to switching to brolucizumab. The characteristics of subjects included in the analysis are summarized in Table 1.

**Functional outcome**

Mean±SD BCVA was 0.43±0.12 LogMAR at T1 and 0.56 ± 0.16 LogMAR at T2 (P=0.038). A significant improvement in BCVA was displayed at T3 (0.56 ± 0.16 LogMAR and 0.34 ± 0.21 LogMAR, p =0.019). A graphical representation of the BCVA changes are summarized in Figure 3.

**Anatomical outcome**
Central macula thickness (CMT) analysis

Significant changes in CMT were displayed among the different study visits. In detail, CMT at T2 was thicker in comparison to T1 values, although this difference did not reach statistically significance (290.4±65.6 μm and 269.1±46.8 μm; P=0.12). On contrary, CMT at T3 was significantly thinner as compared to T2 values (236.8±32.3 μm and 290.4±65.6 μm; P=0.002) (Table 2).

Choroidal analysis

At T2, a significant reduction in both vessel lumen and total area was displayed, as compared to T1 (P=0.032 and P=0.046, respectively). Moreover, both LCA and TCA were increased at T3 as compared with T2 values (P=0.008 and P=0.01, respectively). No differences in SCA and CVI were detected among different visits (P>0.05 in all the comparisons). Similarly, the CT did not show significant differences at each time (P>0.05 in all the comparisons) (Table 2).

Discussion

In this study, using the CMT, CVI and CT analysis, we have analyzed the anatomical fluctuations in eyes treated for neovascular AMD when switched from aflibercept or ranibizumab to brolucizumab. The long-term neovascular AMD management associated with the maintenance of visual acuity still represents an unmet need. The recent approval of brolucizumab has offered a viable treatment option. However, limited data are available on its impact on clinical practice. Herein, we describe functional and anatomical early changes after switch to brolucizumab in clinical routine. Our results indicate that switching to brolucizumab may represent an option in particular for morphological effects in neovascular AMD previously treated with multiple injections of anti-VEGF without sufficient fluid resolution in various anatomical compartments. A significant reduction in CMT was observed at T3 proving an encouraging response on morphological signs of disease activity. In accordance with our study, Bulirsch et al. showed improvement in anatomical outcomes in 63 eyes of 57 patients with neovascular AMD switched to brolucizumab. Other reports also revealed beneficial improvement of various OCT characteristics at first visit following switch to brolucizumab. Furthermore, our findings have displayed significant BCVA changes at T3 compared with T2, this highlighting effective functional improvements after the first brolucizumab injection.

This study was intended to determine the morphological effect of switching to brolucizumab. For this reason, using a novel OCT-based parameter (CVI), we have quantified specific changes in the vascular and total area of the choroid. In detail, T3 (i.e. 1 month after brolucizumab injection) was characterized by a significant LCA and TCA increase, while no significant choroidal changes were detected between T2 and T1. Therefore, based on our results, a significant increase in both vascular and total choroidal areas (i.e., LCA and TCA) was disclosed in patients switched from aflibercept or ranibizumab to brolucizumab. Our results might be associated with different hypotheses. First, we may suggest a possible role of non-vascular smooth muscle cells (NVSMCs), which are abundant in the choroid and influence choroidal
vascular dilation. Assuming that NVSMCs and choroidal vessels have autonomic innervation an increase in short-term sympathetic input after brolucizumab injection can lead to relaxation of these cells and consequent vascular enlargement. Alternatively, an inflammatory process secondary to brolucizumab injection might cause a choroidal vasodilation.

Our findings could be important for monitoring neovascular AMD switched to brolucizumab. Other reports revealed that the loading doses of aflibercept or ranibizumab for treatment-naïve AMD caused a decrease in choroidal thickness. More recently, an OCT multicenter study measured the subfoveal CT after the loading doses of brolucizumab for treatment-naive eyes, reporting that the CT decrease was greater than that reported for other anti-VEGF agents. Noteworthy, it needs to be considered that the authors studied only SCT alterations of 73 eyes affected by different subtype of neovascular AMD. Using OCT-based parameters (CMT, CVI and CT), this is the first study to investigate short-term morphological changes after switching to brolucizumab. The anatomical impact of brolucizumab administration may result in more effective resolution of SRF and IRF, in association with choroidal vascular swelling.

Our study has limitations that should be considered when interpreting our findings. First, our sample size was relatively small, and the study design was cross-sectional. Second, the follow-up period was short. Another possible limitation of the study is that we identified choroidal boundaries manually. Therefore, measurements are potentially subject to intraobserver variability. On the other hand, also the strengths of our study should be kept in mind. For each patient, we examined morpho-functional fluctuations after switching to brolucizumab and established significant short-term visual and anatomical changes. Furthermore, CVI investigation might be influenced by several factors. For this reason, we used a previously reported and validated algorithm.

In conclusion, our study reports the early morpho-functional changes occurring after brolucizumab treatment in patients with neovascular AMD previously treated with other anti-VEGF molecules (i.e. aflibercept or ranibizumab). We demonstrated that this treatment has a significant morpho-functional impact on these eyes, our results providing new insights for better understanding the role of brolucizumab in the treatment of exudative AMD. Additionally, switch to brolucizumab is a valid option and other studies with a long-term follow-up are needed to verify the clinical significance of our findings.

Methods

Study participants

This retrospective study observed the tenets of the Declaration of Helsinki and was approved by the institutional review board of Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro". Patients gave their written consent to participate in the study.

In this study, subjects 55 years of age and older with type 1 MNV in neovascular AMD in at least one eye were identified from the medical records of the ophthalmology department at the Department of
Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro". All the patients received anti-VEGF intravitreal injections of ranibizumab, or aflibercept and were switched to brolucizumab at the discretion of the treating physician in absence of an anatomic response (i.e. absence of OCT sings of exudation) after previous anti-VEGF therapy.

All patients were imaged with the RTVue XR Avanti spectral domain (SD)-OCT (Optovue, Inc., Fremont, CA, USA). The OCT acquisition was performed at the following visits: (i) 1 month before the last intravitreal injection of aflibercept or ranibizumab before switching to brolucizumab (T1), (ii) 1 month after T1 and at the time of switch to brolucizumab injection (T2), and (iii) 1 month after the latter procedure (T3). Furthermore, all patients received a complete ophthalmologic examination, which involved the measurement of Snellen BCVA, IOP, and dilated ophthalmoscopy.

The exclusion criteria included: (i) history of idiopathic or autoimmune uveitis; (ii) infection or inflammation of the both eyes; (iii) history of myocardial infarction or cerebrovascular disease within the last 6 months (iv) the presence of significant cataract; (v) myopia greater than > 3.00 diopters; and (vi) any optic neuropathy, including glaucoma.

Moreover, images with a strength index less than 40, with significant motion artifact or shadowing effect on the choroid were excluded from the analysis.

**Imaging analysis**

Subjects underwent SD-OCT imaging using enhanced depth imaging (EDI) technique (RTVue XR Avanti; version 2016.1.0.26; Optovue, Inc.), between 08:00 and 12:00 a.m.

The main outcome measures were: (1) Central macular thickness (CMT), and (2) choroidal vascularity index (CVI), and choroidal thickness (CT).

CMT was established as the concentric circles centered on the fovea, having diameters of 1 mm (innermost ring/fovea). CMT was recorded with the Optovue software (RTVue XR Avanti; version 2016.1.0.26; Optovue, Inc) in the central 1 mm-diameter circle (Fig. 1).

CVI was investigated using a previously reported algorithm. In brief, we have exported the EDI-OCT horizontal and vertical single line scan passing through the fovea.

Afterwards, the image analysis involved automated binarization of a linear OCT B-scan after delimiting the choroidal boundaries. The borders of the choroid were manually defined as the zone between the Bruch-RPE junction and the sclero-choroidal junction (the upper and lower boundary) and added to the region of interest (ROI) manager. Total choroidal area (TCA) was computed as the total area of the ROI. The images were binarized using the “Niblack's Auto Local threshold” and dark pixels were defined as the luminal choroidal area (LCA), while white pixels were defined as stromal choroidal area (SCA) CVI was obtained as the ratio between LCA and TCA (Fig. 2).
Choroidal thickness (CT) was assessed by two independent retinal specialists (PV and MOG) with the OCT software (Fig. 1). Interobserver agreement was found to be excellent in the CT assessment (0.89 (confidence interval, 0.86–0.90)).

CMT, CVI and CT analysis was performed at each time point (T1, T2 and T3).

**Statistical analysis**

To detect departures from normality distribution, a Shapiro-Wilk’s test was performed for all variables. Means and standard deviation (SD) were computed for all quantitative variables. A Student’s t-test for paired samples was used to compare quantitative variables between following visits. Statistical calculations were performed using Statistical Package for Social Sciences (version 20.0, SPSS Inc., Chicago, IL, USA). The chosen level of statistical significance was p < 0.05.

**Declarations**

**Data Availability statement:** The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

**Meeting presentation:** none.

**Acknowledgements:** None.

**Financial support:** none.

**Conflict of Interest:** None.

**References**


Table 1. The clinical characteristics of subjects included in the analysis. Quantitative data are presented as mean±SD (standard deviation).

<table>
<thead>
<tr>
<th>Variables</th>
<th>CNV type 1 eyes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n=31)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.5 ± 7.5</td>
</tr>
<tr>
<td>Gender (male,%)</td>
<td>13 (41%)</td>
</tr>
<tr>
<td>N° injections before to switch</td>
<td>10.2± 8.34</td>
</tr>
</tbody>
</table>
Table 2. Structural OCT variables and BCVA changes tested at T1, T2 and T3.

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMT (µm)</strong></td>
<td>269.1±46.8</td>
<td>290.4±55.6</td>
<td>236.8±32.3</td>
</tr>
<tr>
<td></td>
<td>p= 0.12</td>
<td>p= 0.002</td>
<td></td>
</tr>
<tr>
<td><strong>LCA mm²</strong></td>
<td>0.676±0.1039</td>
<td>0.641±0.0809</td>
<td>0.683±0.0859</td>
</tr>
<tr>
<td></td>
<td>p= 0.032</td>
<td>p= 0.008</td>
<td></td>
</tr>
<tr>
<td><strong>SCA mm²</strong></td>
<td>0.134±0.0315</td>
<td>0.133±0.0389</td>
<td>0.139±0.0374</td>
</tr>
<tr>
<td></td>
<td>p= 0.934</td>
<td>p= 0.48</td>
<td></td>
</tr>
<tr>
<td><strong>TCA mm²</strong></td>
<td>0.806±0.1082</td>
<td>0.775±0.0991</td>
<td>0.822±0.0854</td>
</tr>
<tr>
<td></td>
<td>p= 0.045</td>
<td>p= 0.01</td>
<td></td>
</tr>
<tr>
<td><strong>CVI (%)</strong></td>
<td>83.3±4.0</td>
<td>82.7±4.7</td>
<td>83.0±4.4</td>
</tr>
<tr>
<td></td>
<td>p= 0.388</td>
<td>p= 0.689</td>
<td></td>
</tr>
<tr>
<td><strong>CT (µm)</strong></td>
<td>245.1±34.8</td>
<td>251.4±41.6</td>
<td>279.8±54.3</td>
</tr>
<tr>
<td></td>
<td>p= 0.341</td>
<td>p= 0.125</td>
<td></td>
</tr>
<tr>
<td><strong>BCVA (logMAR)</strong></td>
<td>0.43±0.12</td>
<td>0.56±0.16</td>
<td>0.34±0.21</td>
</tr>
<tr>
<td></td>
<td>p= 0.033</td>
<td>p= 0.019</td>
<td></td>
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</table>

Data are presented as Mean ± SD. CMT central macular thickness; LCA luminal choroidal area; SCA stromal choroidal area; TCA total choroidal area; CVI choroidal vascularity index; CT choroidal thickness; BCVA best-corrected visual acuity.

*a,b* Paired test *a* comparison T1 versus T2; *b* comparison T2 versus T3.

**Figures**

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Figure 1

Representation of central macular thickness (CMT) and subfoveal choroidal thickness (SFCT) measured at each time (T1, T2 and T3).

CMT was established as the concentric circles centered on the fovea, having diameters of 1 mm (innermost ring/fovea). CMT was recorded with the Optovue software. The SFCT was defined as the distance from the hyperreflective line of Bruch membrane to the innermost hyperreflective line of the choriocapillary interface. SFCT was manually assessed by two independent retinal specialists (PV and MOG).
Illustration of the method used to analyze choroidal vasculature from spectral-domain OCT images of an eye with neovascular AMD.

Structural B-scan OCT passing through the fovea was binarized after defining the choroidal boundaries. The borders of the choroid were manually defined as the zone between the Bruch-RPE junction and the sclero-choroidal junction (the upper and lower boundary). Dark pixels were defined as the luminal choroidal area (LCA), while white pixels were defined as stromal choroidal area (SCA). CVI was obtained as the ratio between LCA and TCA.

Figure 3

Mean BCVA at 3 times

BCVA (logMAR)

0.1

0.4

0.7

1

T1

T2

T3

Figure 3
Box and whisker plots showing analyzed BCVA measurements at each time. The ends of the whiskers represent the minimum and maximum values. Details on P-values for each comparison are reported in table 2.