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ORIGINAL PAPER

Outcome of "treat and monitor" regimen of aflibercept and ranibizumab in macular edema secondary to non-ischemic branch retinal vein occlusion

Francesco Pichi · Ahmed Mohammed Elbarky · Tarek Roshdy Elhamaky

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Abstract
Purpose To compare the efficacy of a modified PRN treatment regimen ("treat and monitor") of aflibercept and ranibizumab in macular edema secondary to non-ischemic branch retinal vein occlusion.
Methods Seventy eyes of 70 patients with treatment naïve branch retinal vein occlusion were enrolled. All patients underwent a comprehensive ophthalmic examination, spectral-domain optical coherence tomography, and fluorescein angiography. Patients were randomized 1:1 to receive intravitreal aflibercept (34 eyes) and ranibizumab (36 eyes) with a "treat and monitor" treatment regimen with monthly follow-up for 12 months. Primary outcome measures included mean change in best corrected visual acuity (BCVA) and central foveal thickness (CFT) at month 12 compared to baseline.
Results At 12 months follow-up, the mean BCVA improved from 0.58 ± 0.13 to 0.20 ± 0.15 logMAR ($P = 0.0003$) in the aflibercept group (mean injections 2.6 ± 1.51) and from 0.52 ± 0.11 to 0.21 ± 0.1 logMAR ($P = 0.0002$) in the ranibizumab group (mean injections 2.8 ± 1.78). No statistical difference between the two groups in terms of the visual acuity gains in eyes with macular edema secondary to non-ischemic BRVO treated with either aflibercept or ranibizumab was observed. Mean CFT reduced from 498 ± 46 to 204 ± 23 μm ($P < 0.0001$) in the aflibercept group and from 488 ± 31 to 212 ± 29 μm ($P < 0.0001$) in the ranibizumab group.
Conclusion "Treat and monitor" regimen is a real-life effective strategy in improving visual acuity after macular edema from branch vein occlusion and in reducing the number of injections.

Keywords Intravitreal · Aflibercept · Ranibizumab · Macular edema · Non-ischemic BRVO

Abbreviations

BRVO	Branch retinal vein occlusion
VEGF	Vascular endothelial growth factor
IVA	Intravitreal aflibercept injection
IVR	Intravitreal ranibizumab injection
BCVA	Best corrected visual acuity
CFT	Central foveal thickness
SD-OCT	Spectral-domain optical coherence tomography

F. Pichi (✉)
Eye Institute, Cleveland Clinic Abu Dhabi,
PO Box 112412, Al Maryiah Island, Abu Dhabi, UAE
e-mail: ilmiticopicchio@gmail.com

F. Pichi
Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH, USA

A. M. Elbarky · T. R. Elhamaky
Faculty of Medicine, Benha University, Banha, Egypt

Introduction

Branch retinal vein occlusion (BRVO) is a common retinal vascular disease [1, 2]. Occlusion of the major veins of the retinal circulation leads to an elevation of the vitreous and aqueous vascular endothelial growth factor (VEGF) [3, 4]. Increased VEGF results in higher vascular permeability and associated macular edema in patients with BRVO [5, 6].

Macular edema secondary to retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy [7, 8].

Historically, the gold standard of treatment for patients with macular edema associated with BRVO was grid laser photocoagulation [9]. However, inhibitors of VEGF have revolutionized its treatment [10, 11]. Intravitreal injections of anti-VEGF can now effectively lower levels of intraocular VEGF and reduce vascular permeability [12–15].

Ranibizumab is a humanized monoclonal antibody fragment (Fab) that binds VEGF while aflibercept is a recombinant fusion protein consisting of VEGF-binding receptors 1 and 2 fused into the Fc portion of human immunoglobulin G [19]. Ranibizumab has an aqueous elimination half-life in human eyes of 7.19 days [20]. Among anti-VEGF agents, aflibercept displays a prolonged VEGF inhibition in comparison with the other VEGF antagonists (ranibizumab and bevacizumab) in retinal pigment epithelium/choroid organ cultures. Morphological changes (macular edema) precede functional impairment (visual acuity); thus, close monitoring of patients is warranted after initial anti-VEGF therapy to treat as soon as macular edema reoccurs [17, 18].

Different treatment regimens have been evaluated in the treatment of macular edema secondary to BRVO. In SHORE and HORIZON studies, there was no superiority in pro re nata (PRN) versus monthly treatment. The treat and extend regimen is another regimen option in clinical practice and has been shown to reduce treatment burden and associated costs. However, long-term follow-up data from the RETAIN study demonstrated that 50% of eyes still required anti-VEGF injections at regular intervals [21]. All treatment regimens are associated with a loading phase of three consecutive monthly injections. In fact, inhibition of VEGF after a single aflibercept application of 125 µg/mL can be found over the course of 7 days, with some VEGF detectable at the seventh day. In contrast, VEGF is detectable after 72 h of ranibizumab treatment and some VEGF can already be found 12 h after bevacizumab treatment [16].

In this study, we compared the efficacy of individualized "treat and monitor" regimen of aflibercept and ranibizumab in macular edema secondary to non-ischemic branch retinal vein occlusion. This treatment regimen consists of a modified PRN regimen, where the loading phase is not performed, thus mirroring a real-life clinical situation.

Methods

This is an IRB-approved prospective study of patients with fovea-involved macular edema secondary to non-ischemic branch retinal vein occlusion performed at Sheikh Khalifa Medical City (SKMC). The study was approved by the Institutional Review Board, complied with the Health Insurance Portability and Accountability Act of 1996, and followed the tenets of the Declaration of Helsinki.

Patient selection

Inclusion criteria Patients were enrolled if at least 18 years of age with treatment naïve, fovea-involved macular edema secondary to non-ischemic branch retinal vein occlusion as detected by baseline fluorescein angiography (FA); patients should have a best corrected visual acuity (BCVA) $\leq$ 20/40 or central foveal thickness (CFT) $\geq$ 250 µm detected by spectral-domain optical coherence tomography (SD-OCT).

Exclusion criteria Patients were excluded if FA showed ischemic BRVO, if there was a history of previous intravitreal injections (anti-VEGF, triamcinolone acetonide or dexamethasone implant), or if ocular history was positive for other causes of maculopathy such as diabetic macular edema and age-related macular degeneration.

Eligible patients were randomized by means of sequentially numbered envelopes according to a computer-generated code list and stored by an investigator, unaware of the purpose of the study. A permuted block randomization was performed with a final allocation ratio of 1:1 to intravitreal injection of ranibizumab or aflibercept in the affected eye.

Clinical investigations

A complete ophthalmic examination was undertaken in all patients at baseline and monthly follow-up. Logarithm of the minimum angle of resolution BCVA was determined at 4 m using standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Lighthouse, New York, NY) by a single well-trained and experienced orthoptist, who was masked to the study. Baseline examination and all subsequent monthly follow-up visits included measurement of best corrected visual acuity (BCVA) by Snellen chart, slit-lamp bio-microscopy, intraocular pressure measurement using Goldman applanation tonometry, and dilated funduscopic examination.

Imaging

Central foveal thickness (CFT) was measured in the central 1 mm subfield of all eyes using the optical coherence tomography Spectralis OCT (version 5.1.3.0; Heidelberg Engineering, Heidelberg, Germany) at baseline as well as at the time of first injection and at each subsequent follow-up visit. All OCT scans were qualitatively evaluated for the presence or absence of intra- or sub-retinal fluid by an unmasked retina specialist (A.M.E.). Fluorescein angiography was performed using scanning laser ophthalmoscopy (HRA, Heidelberg, Germany) at baseline to rule out ischemia and repeated at months 3 and 9.

Treat and monitor regimen

This treatment regimen did not require loading phase of three consecutive monthly injections. After randomization, all patients received a baseline intravitreal injection of aflibercept (Eylea; Regeneron, Tarrytown, NY) 2 mg/0.05 mL or ranibizumab (Lucentis, Genentech, South Francisco, CA) 0.5 mg/0.05 mL. Patients were subsequently followed up every 4 weeks. The decision to reinject was taken by the investigator on the basis of the CFT change, and the report submitted separately by the BCVA examiner. Re-treatment was initiated if the BCVA was less than 20/20 or CFT more than 250 μm.

Injection technique

Before injection, topical anesthesia was induced by tetracaine 1% eyedrops. Povidone-iodine was applied to the eyelid margins and the lashes. A lid speculum was inserted, and povidone-iodine 5% was applied to the conjunctiva bulbi and the fornices for at least 3 min. A volume of 0.05 mL (0.5 mg of ranibizumab and 2 mg of aflibercept) was injected through a 30-gauge needle at 3.5–4 mm of inferotemporal limbus.

Primary outcome measures Included mean change in BCVA and CFT at month 12 compared to baseline.

Statistical analysis

Visual acuity was measured as logMAR (logarithm of the minimum angle of resolution) for statistical analysis. To analyze changes in BCVA and CFT, paired Student's t test was used. A P value less than 0.05 was considered statistically significant.

Results

Study population

Seventy eyes of 70 patients were enrolled in this prospective study. A total of 34 patients were randomized to the intravitreal aflibercept 2 mg/0.05 mL group and 36 patients to the intravitreal ranibizumab 0.5 mg/0.05 mL.

The study population was similar between the two groups. The mean age of patients was 54.8 ± 4.4 years with 18 males (52.9%) and 16 females (47%) in the intravitreal aflibercept group (IVA) and 55.8 ± 4.9 years with 20 males (55.5%) and 16 (44.4%) females in the intravitreal ranibizumab group (IVR).

Functional and anatomical outcomes

The mean numbers of aflibercept and ranibizumab injections were 2.6 ± 1.51 and 2.8 ± 1.78, respectively ($P = 0.8$). No re-treatment after the baseline injection was needed for ten (40%) eyes in aflibercept group and 11 (38%) eyes in ranibizumab group (Table 1).

Table 1 Comparison of data between intravitreal aflibercept and ranibizumab injections for macular edema secondary to BRVO

	IVA	IVR
BCVA baseline (logMAR)	0.58 ± 0.13	0.52 ± 0.11
BCVA 1 month follow-up (logMAR)	0.25 ± 0.12	0.25 ± 0.11
BCVA 12 months follow-up (logMAR)	0.20 ± 0.15	0.21 ± 0.1
CFT baseline (μm)	498 ± 46	488 ± 31
CFT 1 month follow-up (μm)	228 ± 23	225 ± 19
CFT 12 months follow-up (μm)	204 ± 23	212 ± 29
Number of injections	2.6 ± 1.51	2.8 ± 1.78

In the aflibercept group, mean BCVA improved significantly from 0.58 ± 0.13 logMAR at baseline to 0.25 ± 0.12 after the first injection ($P = 0.0005$). Final BCVA at 12 months was 0.20 ± 0.15 logMAR ($P = 0.0003$). Mean CFT reduced significantly from 498 ± 46 μm at baseline to 228 ± 23 μm at 1 month, and final CFT was 204 ± 23 μm at 12 months follow-up ($P < 0.0001$). The representative SD-OCT changes of CFT of a case in the aflibercept group are shown in Fig. 1 (a: baseline, b: 1-month post-injection, c: 12 months post-injection).

In the ranibizumab group, mean BCVA improved significantly from 0.52 ± 0.11 logMAR at baseline to 0.25 ± 0.11 and 0.21 ± 0.1 logMAR at 1 and 12 months follow-up ($P = 0.0007$ and 0.0002, respectively). The mean CFT reduced significantly from a mean baseline of 488 ± 31 μm to 225 ± 19 μm after the first injection; final CFT at 12 months was 212 ± 29 ($P < 0.0001$) (Figs. 2, 3). The representative SD-OCT changes in CFT of a case in the ranibizumab group are shown in Fig. 4 (a: baseline, b: 1-month post-injection, c: 12 months post-injection).

Overall, 86.52% of the reduction in CFT from baseline was reached by month 1 (270 ± 23 μm) and (263 ± 16 μm) in the aflibercept and ranibizumab groups, respectively. There was no statistical difference between the two groups in terms of CFT and BCVA improvement ($P > 0.05$).

Safety

Regarding ocular side effects, no severe ocular adverse events were reported. The most common side effect was subconjunctival hemorrhage at the site of injection.

Regarding systemic safety, no serious systemic adverse events were reported.

Discussion

Anti-VEGF drugs have revolutionized the management of BRVO-associated macular edema.

VEGF was proved as a major mediator for macular edema in BRVO. Many previous studies have concluded the resolution of macular edema and improvement of vision in response to anti-VEGF drugs [22–25].

The burden of anti-VEGF injection on the health care system is a well-known concern. Considering pathophysiology and the natural course of non-ischemic BRVO as a self-limited disease, in our study we followed a treat and monitor regimen which is a modified PRN regimen that better applies to day-to-day clinical practice in the management of macular edema secondary to non-ischemic BRVO aiming to achieve the maximum visual gain with the least number of injections.

During 12 months of this perspective study, the mean numbers of aflibercept and ranibizumab injections performed were 2.6 ± 1.51 and 2.8 ± 1.78, respectively.

Our results showed improvement in the mean BCVA to 0.20 ± 0.15 and 0.21 ± 0.1 logMAR and reduction in the mean CFT to 204 ± 23 and 212 ± 29 μm after one-year "treat and monitor" treatment regimen of aflibercept and ranibizumab, respectively. This improvement was maintained at month 12.

Although precise comparisons between studies are difficult, the mean number of injections over 12 months in our study was significantly lower than other trials that followed different treatment regimens; in the "VIBRANT," "BRIGHTER," and "BRAVO" trials, the mean number of injections was 5.7, 4.8, and 5.7 over 6 months follow-up, respectively. Tan et al. showed 8.1 as the mean number of injections required

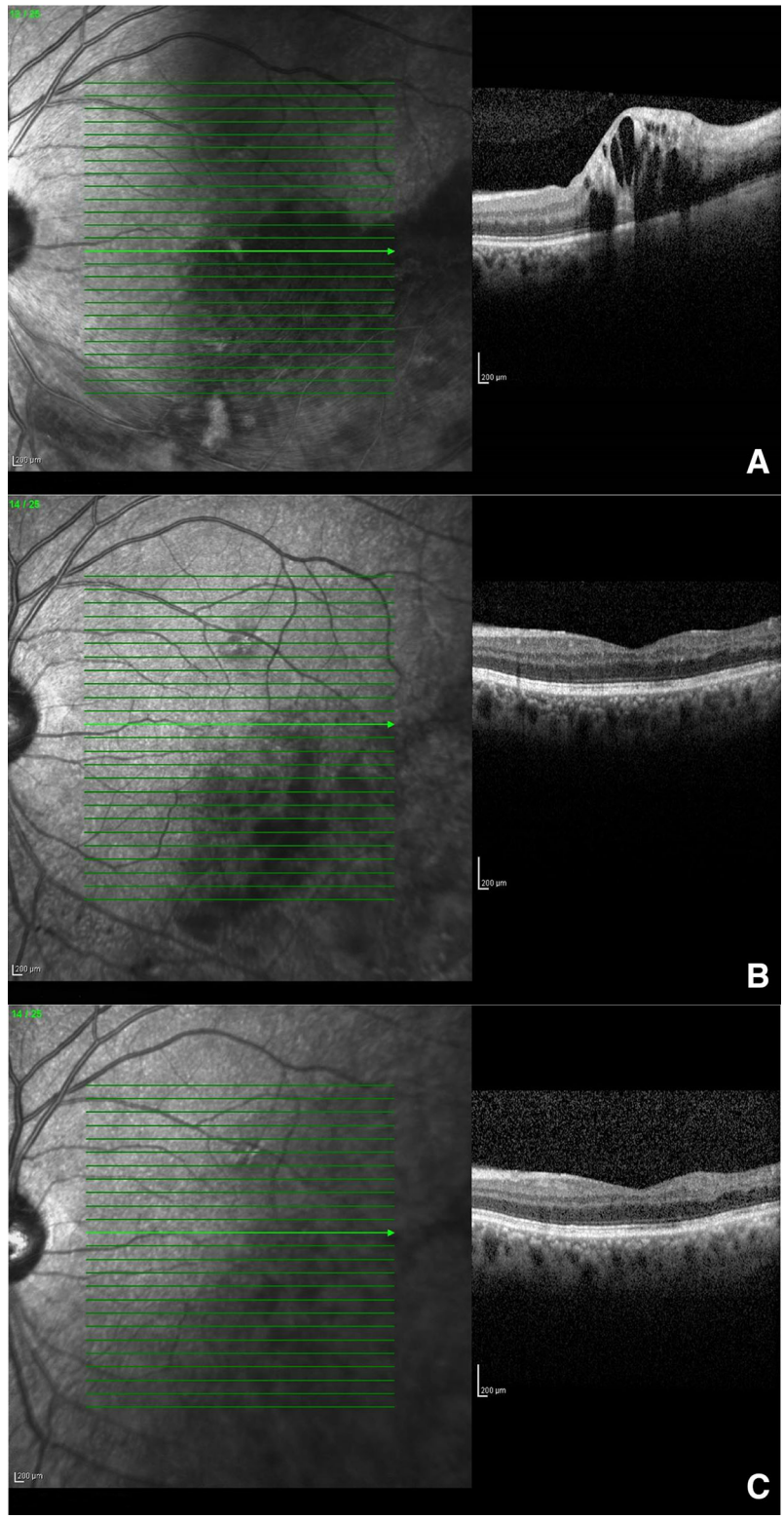
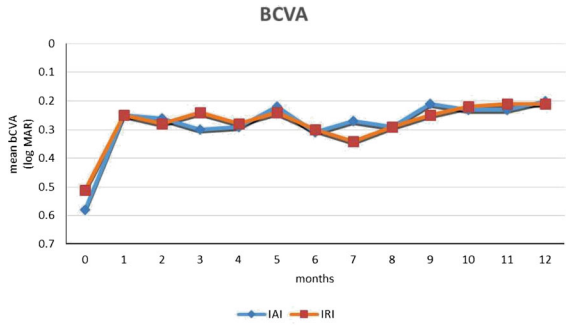
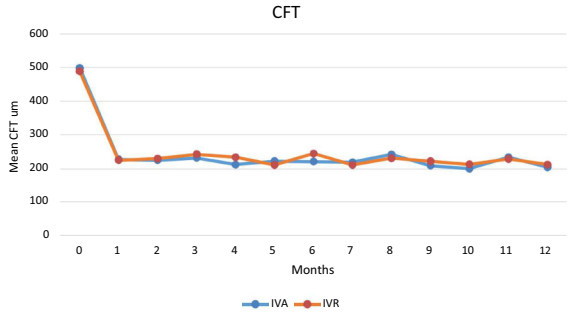


Fig. 1 **a** Spectral-domain optical coherence tomography imaging (SD-OCT) picture of the left eye of 55 years old male patient showing macular edema secondary to inferior branch retina vein occlusion (BRVO) with best corrected visual acuity (BCVA) of 20/50, before intravitreal aflibercept injection. **b** Spectral-domain optical coherence tomography imaging (SD-OCT) picture of the same patient showing complete resolution of the macular edema, 1 month post-intravitreal aflibercept injection (IAI) with BCVA of 20/25. **c** Spectral-domain optical coherence tomography imaging (SD-OCT) picture of the same patient, 12 months post intravitreal aflibercept injection (IAI), with BCVA of 20/20



BCVA: Best corrected visual acuity
IVR: Intravitreal Ranibizumab injection
IVA: Intravitreal Aflibercept injection

Fig. 2 Best corrected visual acuity change over 12 months in the ranibizumab (0.31 ± 0.1 logMAR) and aflibercept (0.38 ± 0.15 logMAR) "treat and observe" groups



CFT: Central foveal thickness
IVR: Intravitreal Ranibizumab injection
IVA: Intravitreal Aflibercept injection

Fig. 3 Mean change in central foveal thickness over 12 months in the ranibizumab (276 ± 23 μm) and aflibercept (294 ± 29 μm) "treat and observe" groups

over 12 months [26]. This remarkable fewer number of injections in our study could be explained by exclusion of ischemic BRVO.

Preti et al. and Wang et al. reported improvement in best corrected visual acuity (BCVA) after just a single intravitreal injection of bevacizumab and aflibercept, respectively, in BRVO associated with macular edema [27, 28].

As far as efficacy of aflibercept and ranibizumab in reducing macular thickness and improving visual acuity, our results are similar to prior studies on BRVO-associated macular edema.

The BRAVO study included eyes diagnosed with BRVO within 12 months of study entry and a BCVA between 20/40 and 20/400 with CFT ≥ 250 μm as assessed by OCT. Mean ETDRS letter score improvement was 16.6 and 18.3 in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, and 7.3 in the sham group. CFT decreased by a mean of 337 μm (0.3 mg) and 345 μm (0.5 mg) in the ranibizumab groups, which was greater than the 158 μm reduction in the sham group [29].

Sakanishi et al., who assessed the efficacy of intravitreal ranibizumab, found that the visual acuity and central retinal thickness were improved in BRVO at 6 months. Even more importantly, they concluded that the thinner the central foveal thickness prior injection, the higher the rate of sustained effect following a single dose [30].

In a study by Narayanan et al., the mean gains in BCVA were +18.1 letters in the ranibizumab group and +15.6 letters in the bevacizumab group at 6 months. Mean reductions in CRT was 177.1 ± 122.3 μm in the ranibizumab group and 201.7 ± 166.2 μm in the bevacizumab group, with no significant difference between the two groups [31].

In 2015, a multicenter randomized trial (VIBRANT) compared intravitreal aflibercept and focal laser for BRVO-associated macular edema [19]. Mean ETDRS letter improvement score was 17.0 in the aflibercept versus 6.9 in the laser group at 24 weeks. Mean reduction in CFT was 280.5 μm in the aflibercept versus 128 μm in the laser group. The study concluded that intravitreal aflibercept is an effective treatment for BRVO-associated macular edema. Contrary to BRAVO, in which after the first 6 months patients were shifted to a PRN regimen, VIBRANT treated its participants every 8 weeks until month 12 [22].

The efficacy of aflibercept for anatomical and functional recovery was similar to that reported for other anti-VEGF agents used as treatment for macular edema-associated BRVO and better than the sham group or laser-only treatments described in previous studies [32].

It may be tempting to compare trial results of BRAVO and VIBRANT to find whether ranibizumab or aflibercept is superior. A meta-analysis concluded equivalent efficacy of both drugs based on the available studies. However, nonequivalent endpoints as well as different inclusion and exclusion criteria make this comparison difficult [33, 34].

Our study demonstrated no statistical difference between the two groups in terms of visual acuity gains in eyes with macular edema secondary to non-

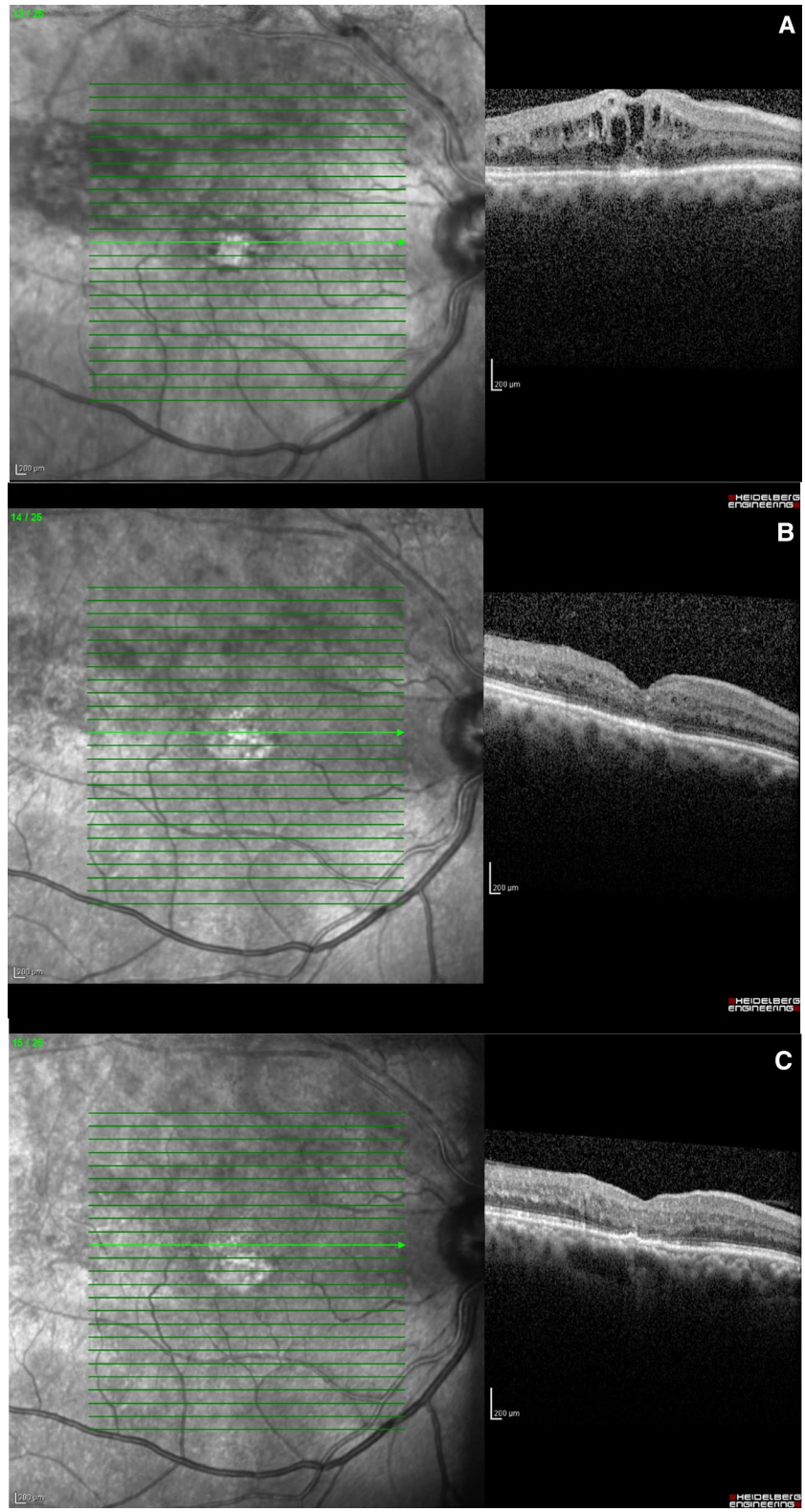


Fig. 4 **a** Spectral-domain optical coherence tomography imaging (SD-OCT) picture of the right eye of 53 years old female patient showing macular edema secondary to superior branch retina vein occlusion (BRVO), with best corrected visual acuity (BCVA) of 20/60, before intravitreal ranibizumab injection. **b** Spectral-domain optical coherence tomography imaging (SD-OCT) picture of the same patient showing complete resolution of the macular edema, 1 month post-intravitreal ranibizumab injection (IRI), with BCVA of 20/30. **c** Spectral-domain optical coherence tomography imaging (SD-OCT) picture of the same patient, 12 months post-intravitreal ranibizumab injection (IAI), with BCVA of 20/25

ischemic BRVO treated with either aflibercept or ranibizumab. The main limitation of our study includes the small cohort of patients. We showed that "treat and monitor" regimen is an effective strategy in improving and maintaining the visual gain over the course of 12 months with fewer number of injections, hence decreasing the burden of anti-VEGF therapy on the health care system. However, a longer follow-up is needed to verify that these improvements are maintained after the first year.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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