INTRODUCTION

Branch retinal vein occlusion (BRVO) is the second most common retinal sight-threatening vascular disorder, the frequency of which is surpassed only by diabetic retinopathy (1-3). The occlusion usually develops in an arteriovenous nicking, where both vessels share the adventitia. The visual acuity (VA) decreases because of concurrent retinal hemorrhages, macular ischemia, and macular edema (ME), which is the most frequent factor that affects vision in the short, intermediate, and especially long term. Several therapeutic approaches have been proposed for BRVO ranging from isovolemic hemodilution to vitrectomy (4-10). Since publication of the Branch Vein Occlusion Study Group results in 1984, in which investigators found a significant mean improvement of 1.33 lines of vision com-
metamorphopsia or decreased VA ranging from 0.1 to 0.5 assessed with 6-meter Snellen charts. All patients had multiple hemorrhages in the affected BRVO areas and ME assessed by spectral domain optical coherence tomography (SD-OCT) (fig. 1). The Ethics Committee of our hospital approved the study, which was conducted in accordance with the tenets of the Declaration of Helsinki. All patients provided informed consent before entering the study. At the first visit, all patients underwent a standard ophthalmic evaluation of best-corrected visual acuity (BCVA) with 6-meter Snellen charts and SD-OCT imaging with a macular cube 256 × 128 scan protocol (Cirrus HD-OCT®, Carl Zeiss Meditec, Dublin, CA, USA). The tomographic parameter analyzed in this study was the central subfield thickness (CST), which was measured at baseline and 1, 3, 6, and 12 months after treatment (fig. 2). The main outcome measures were BCVA and CST for all visits during the study period.

Intravitreal injections of 1.25 mg of bevacizumab (Avastin®, Genentech Inc., South San Francisco, CA, USA) in a 0.05-mL volume were administered in the clinic. After instilling 0.23 line in controls after 3 years of follow-up with a level of evidence A, grid laser photoacoagulation has been considered the gold standard for treating ME in patients with BRVO (6). Recently, alternative therapies, i.e., intravitreal injections of corticosteroids, anti-vascular endothelial growth factor (VEGF) drugs, or new devices for extended drug release such as dexamethasone implants, have been proposed, sometimes in combination treatment protocols that have not provided definitive medium- and long-term results. We propose a previously unreported alternative treatment based on combination treatment with intravitreal antiangiogenic therapy and macular grid laser photoacoagulation of the affected areas in a series of patients with ME associated with BRVO.

METHODS

Eight eyes of 8 patients with ME secondary to BRVO and decreased VA were prospectively included between May and November 2008. Every patient had had at least 3 months of evolution since symptom onset, described as metamorphopsia or decreased VA ranging from 0.1 to 0.5 assessed with 6-meter Snellen charts. All patients had multiple hemorrhages in the affected BRVO areas and ME assessed by spectral domain optical coherence tomography (SD-OCT) (fig. 1). The Ethics Committee of our hospital approved the study, which was conducted in accordance with the tenets of the Declaration of Helsinki. All patients provided informed consent before entering the study. At the first visit, all patients underwent a standard ophthalmic evaluation of best-corrected visual acuity (BCVA) with 6-meter Snellen charts and SD-OCT imaging with a macular cube 256 × 128 scan protocol (Cirrus HD-OCT®, Carl Zeiss Meditec, Dublin, CA, USA). The tomographic parameter analyzed in this study was the central subfield thickness (CST), which was measured at baseline and 1, 3, 6, and 12 months after treatment (fig. 2). The main outcome measures were BCVA and CST for all visits during the study period.

Intravitreal injections of 1.25 mg of bevacizumab (Avastin®, Genentech Inc., South San Francisco, CA, USA) in a 0.05-mL volume were administered in the clinic. After instilling 0.5% proparacaine hydrochloride topical eyedrops 3 times every 5 minutes for topical anesthesia, the eye was irrigat-
ed with 5% povidone iodine, opened using a lid retractor, and the drug was injected through the pars plana 3.0 mm posterior to the limbus in pseudophakic eyes and 3.5 mm posterior to the limbus in phakic eyes using a 30-gauge needle. After every intravitreal injection, an ophthalmic solution of topical ofloxacin (Exocin®, Allergan Pharmaceuticals Ltd., Ireland) was administered 4 times daily for 1 week. Intravitreal bevacizumab (IVB) injections were administered at baseline in all patients; reinjections were administered if persistent or recurrent intraretinal fluid (cysts) was observed in SD-OCT.

Laser application was performed with a pan-funduscopic TransEquator® lens (Volk Optical Inc., Mentor, OH, USA) (spot diameter, 50 µm; exposure time, 200 ms; power, 80-100 mW) until soft whitening of the retina became apparent, according to physician discretion. Grid laser photocoagulation was performed over the area of ME. Laser spots were not applied a minimum of 500 µm from the foveal center. Laser was applied 1 month after the first IVB injection in all cases. One patient (case 2) underwent sectorial laser photocoagulation at baseline due to peripheral ischemia observed on fluorescein angiography. No additional macular grid laser photocoagulation was performed during follow-up in any case.

Statistical analysis was performed with SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). Fisher exact test was used to assess baseline and post-treatment differences in VA and central subfield thickness (CST) at all time points. The significance level was p≤0.05.

RESULTS

The mean patient age was 71.6±7.68 (mean ± standard deviation) years. The demographic features and individual patient data are shown in Table I. The mean baseline BCVA

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Best-corrected visual acuity</th>
<th>Central subfield thickness</th>
<th>Doses</th>
<th>Months post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline 1 mo 3 mo 6 mo 12 mo</td>
<td>Baseline 1 mo 3 mo 6 mo 12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>76</td>
<td>M</td>
<td>0.4 0.7 0.8 0.8 0.8</td>
<td>545 190 182 370 305</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>F</td>
<td>0.15 0.4 0.6 0.6 0.7</td>
<td>494 346 327 304 221</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>0.10 0.4 0.4 0.4 0.5</td>
<td>737 236 362 370 393</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>F</td>
<td>0.4 0.6 0.4 0.8 0.8</td>
<td>361 281 359 355 311</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>F</td>
<td>0.3 0.7 0.9 0.9 0.9</td>
<td>362 292 253 249 251</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>M</td>
<td>0.5 0.5 0.5 0.6 0.5</td>
<td>497 371 560 348 461</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>F</td>
<td>0.2 0.2 0.5 0.5 0.5</td>
<td>534 341 378 486 515</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>M</td>
<td>0.2 0.3 0.4 0.4 0.4</td>
<td>305 304 247 230 230</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td>71.63</td>
<td></td>
<td>0.28 0.47 0.56 0.65 0.66</td>
<td>479.38 295.13 333.50 339.00 335.88</td>
<td>2.13</td>
<td>2.71</td>
</tr>
<tr>
<td>SD</td>
<td>7.68</td>
<td></td>
<td>0.14 0.18 0.19 0.16 0.15</td>
<td>137.52 60.10 114.45 80.24 109.66</td>
<td>0.83</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Demographics and individual features of patients included in the study. Best-corrected visual acuity and central subfield thickness assessed by spectral domain optical coherence tomography at baseline, month 1, month 3, month 6, and month 12 post-treatment; total number of intravitreal bevacizumab (IVB) doses per eye and months post-treatment in which 2nd dose of IVB was performed (if required).

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Mean best-corrected visual acuity</th>
<th>p</th>
<th>Mean central subfield thickness</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.28</td>
<td></td>
<td>479.38</td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>0.47</td>
<td>0.031*</td>
<td>295.13</td>
<td>0.008*</td>
</tr>
<tr>
<td>3 mo</td>
<td>0.56</td>
<td>0.031*</td>
<td>333.50</td>
<td>0.070</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.65</td>
<td>0.008*</td>
<td>339.00</td>
<td>0.008*</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.68</td>
<td>0.016*</td>
<td>335.88</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

Mean best-corrected visual acuity and mean central subfield thickness assessed by spectral domain optical coherence tomography at baseline, month 1, month 3, month 6, and month 12 post-treatment. *p≤0.05.
was 0.28±0.14 Snellen, and at 1, 3, 6, and 12 months after treatment the BCVA levels were 0.47±0.18 (p=0.031), 0.56±0.50 (p=0.031), 0.65±0.60 (p=0.008), and 0.66±0.65 (p=0.016), respectively (Tab. II). The mean baseline CST was 479±137 µm; 1, 3, 6, and 12 months after treatment the mean CST values were 295±60 µm (p=0.008), 333±114 µm (p=0.070), 339±80 µm (p=0.008), and 335±109 µm (p=0.008) (Tab. II). The mean number of injections was 2.13±0.83. In 7 patients who required a second injection, the injection was administered a mean of 2.71 months (SD 0.75) after the first dose. One patient required 4 injections during follow-up, and another patient did not receive additional treatment.

DISCUSSION

Intravitreal bevacizumab associated with grid laser photocoagulation decreased the CRT assessed by SD-OCT and improved the VA in patients with ME secondary to BRVO. After the first IVB injection, a decrease in the CRT was observed in all cases associated with an increase in the VA before and after grid laser photocoagulation. We did not observe the same effect with the second injection administered at about month 3 of follow-up, 2 months after grid laser photocoagulation. Although the CRT did not steadily decrease after the second IVB injection, the VA improvement was sustained from the third month through the remainder of the follow-up period. Thus, from the 3-month evaluation, we did not find a good correlation between the VA and the CRT, which agreed with the results of previous studies with a larger number of patients with ME secondary to BRVO (1). However, this unexpected discrepancy suggested that other factors may be involved, i.e., the integrity of the junction between the inner and outer photoreceptor segments on SD-OCT, the volume of intraretinal cysts, or retinal pigment epithelium atrophy. Unfortunately, assessment of the influence of these factors in our results exceeds the limitations of this study.

The treatment of ME secondary to BRVO has been controversial (2, 3). Ranging from isovolemic hemodilution (4) to vitrectomy with sheathotomy (6) of the arteriovenous nicking, therapies such as laser grid photocoagulation or intravitreal drug injections have not provided definitive satisfactory, evidence-based results. Since the Branch Vein Occlusion Study Group published its results in 1984, grid laser photocoagulation has been the gold standard treatment for ME in patients with BRVO. In the current study, a gain of 2 lines of vision was observed at 8 months in 65% of patients; that increase was 1.3 lines 3 years after laser application (6). These results have not been clearly surpassed by other treatments in comparably designed studies. Several authors have considered surgery as a treatment for ME associated with BRVO. Pars plana vitrectomy with posterior hyaloidectomy and sheathotomy of the arteriovenous nicking resolved the ME in different series (7-9). Whereas the technical difficulty of the surgery was the main limitation, other authors have suggested that sheathotomy was unnecessary and showed similar results in a comparative study (10). Nevertheless, the inherent inconvenience of surgery and the limited surgical results have shifted the focus to other less-invasive therapies.

The development of pharmacologic intravitreal treatment has been remarkably in recent years, and these drugs currently are used routinely to treat diverse retinal pathologies. Intravitreal injection of corticosteroids, especially triamcinolone acetonide (TA), has been widely used to treat ME with diverse etiologies, including BRVO. Several authors have reported good short- and intermediate-term VA results with TA (11-15). Unfortunately, these studies had small numbers of patients and frequently lacked a control group for comparison. The findings cannot be considered definitive and larger studies must confirm them. More recently, the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study, which included a large number of patients and a 12-month follow-up period, reported that intravitreal injection of TA did not obtain better results than those in the control group treated with grid laser photocoagulation (16). However, other studies have compared TA use combined with grid laser photocoagulation and obtained acceptable results in short series (17, 18), but problems related to intravitreal administration, i.e., glaucoma, cataract development, or noninfectious endophthalmitis, and the fact that TA administration is an off-label use, have reduced physician interest in this treatment. To overcome these problems, new corticosteroid delivery devices have been developed. The dexamethasone implant, which was approved recently by the Food and Drug Administration for use in patients with BRVO, has reduced the risk of vision loss and improved the speed and incidence of visual improvement at 6 months compared to sham controls with moderate adverse effects (19-21). Although these results have been promising, they must be ratified in further reports with longer follow-up periods.
In the last decade, the results achieved with anti-VEGF drugs in age-related macular degeneration and the suggested role of VEGF in the development of ME secondary to vascular pathologies have led to a hypothesis about their effectiveness. Therefore, several studies have been performed to assess ranibizumab (Lucentis®, Genentech Inc.), bevacizumab, and pegaptanib (Macugen®, Pfizer/Eyetech Pharmaceutical) on ME in patients with BRVO (22-26). Most studies have been uncontrolled, nonrandomized short case series, and it is impossible to make reliable comparisons among them. However, Campochiaro and the BRAVO Study Group recently reported significant visual improvement with intravitreal ranibizumab compared to sham injection at 6 months, with a lower rate of rescue grid laser than controls and no increased adverse effects (27). The medium- and long-term data of this study will provide important information about its role in clinical practice.

The clinical observation that antiangiogenic drugs, specifically bevacizumab, effectively decreased the ME associated with BRVO led to the current study. The aim of our study was to add a beneficial transient effect over the vascular permeability of IVB to the long-term macular stabilization provided by grid laser photocoagulation. Although the mechanism of this laser-related beneficial effect remains unknown and several hypotheses have been proposed, we consider that the benefit may be due to retinal pigment epithelium stimulation. To our knowledge, this is the first study to propose this sequential combination treatment in a series of patients with ME associated with BRVO. The results obtained were promising, but the small number of patients, the lack of a control group, and the limited 12-month follow-up period does not permit us to draw definitive conclusions. However, the results of this study are a well-founded basis to develop further studies involving a larger number of patients to confirm these results. In conclusion, the findings suggested that combination treatment comprised of IVB and grid laser photocoagulation may be an alternative option for these patients.

Proprietary interest: None.

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