Navigated laser and aflibercept versus aflibercept monotherapy in treatment-naïve branch retinal vein occlusion: A 12-month randomized trial

Katrine Hartmund Frederiksen,1,2 Jesper Pindbo Vestergaard,1 Frederik Norregaard Pedersen,1,2 Anna Stage Vergmann,1 Torben Lykke Sorensen,3,4 Caroline Schmidt Laugesen,3 Ryo Kawasaki,2,5 Tunde Peto2,6 and Jakob Grauslund1,2

1Department of Ophthalmology, Odense University Hospital, Odense, Denmark
2Department of Clinical Research, University of Southern Denmark, Odense, Denmark
3Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark
4Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark
5Department of Vision Informatics, Osaka University School of Medicine, Osaka, Japan
6School of Medicine, Dentistry and Biomedical Sciences, Queen’s University, Belfast, UK

ABSTRACT.

Purpose: Angiostatic agents have proven effective in the treatment of macular oedema in patients with branch retinal vein occlusion (BRVO). However, treatment is inconvenient and expensive, and novel treatment regimens are warranted. We aimed to evaluate if combination treatment of navigated central retinal laser and aflibercept lowered the treatment burden in these patients.

Methods: Treatment-naïve patients with BRVO and macular oedema were included at two centres and randomized 1:1 to three monthly injections of 2.0 mg aflibercept with (Group A) or without (Group B) navigated central laser, followed by aflibercept as needed from month 4 through 12. Re-treatment need was evaluated, and secondary endpoints included functional and anatomical outcomes and safety evaluated by retinal microperimetry.

Results: We evaluated 41 eyes of 41 patients with a mean age of 69.6 years. Baseline median best-corrected visual acuity (BCVA) was 70.0 letters, and median central retinal thickness (CRT) was 502 μm with no difference between Groups A (n = 21) and B (n = 20). Percentage of patients needing re-treatment after month three was 71% and 80% (p = 0.72). At month 12, groups did not differ in number of injections after loading (1 versus 2, p = 0.43), change in BCVA (+12.8 versus +15.1 letters, p = 0.48), CRT (–195 versus –181 μm, p = 0.82), or retinal sensitivity (+3.3 versus +4.1 dB, p = 0.67).

Conclusion: In treatment-naïve BRVO patients, addition of navigated central laser to aflibercept did not lower treatment burden or affect functional or anatomical outcomes. A low number of intravitreal injections were needed for successful outcome in both treatment arms.

Key words: aflibercept – branch retinal vein occlusion – macular oedema – navigated central retinal laser – randomized clinical study – vascular endothelial growth factor inhibition

The study was supported by grants from Danish Regions; Fight for Sight, Denmark - Bagenkop Nielsens Ojen-Fond; The Synoptik Foundation, Denmark; Fabrikan Einar Willumsens Mindelegat; The Research Fund for Region Seeland and Region of Southern Denmark; Toyota-Fonden, Denmark; Grosserer Chr. Andersen og husbru Ingeborg Andersen, f. Schmidts legat; Odense University Hospital – The PhD Fund for operating costs and The OUH Fund for Free Research and The A.P. Møller Foundation for the Advancement of Medical Science. The funders had no influence on the study.

We thank all funders for the granted support. We also thank the study nurses at Odense University Hospital and Roskilde University Hospital for help conducting patient visits, and the Departments of Ophthalmology at Odense University Hospital and Roskilde University Hospital for providing equipment and facilities for the study.

JG declares participation in the Advisory Board for Bayer, Novartis, Allergan and Roche. RK declares participation in the technical advisory for Office Future, and research funding support from Topcon (endowed professorship), Novartis, Senju, Nanolux and Tamron. KHF, JPV, FNP, ASV, TLS, CSL and TP declare no conflicts of interest.

Acta Ophthalmol. 2022: 100: e1503–e1509
© 2022 The Authors. Acta Ophthalmologica published by John Wiley & Sons Ltd on behalf of Acta Ophthalmologica Scandinavica Foundation. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

doi: 10.1111/aos.15182
Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disorder and a leading retinal cause of blindness (Song et al. 2019). Branch RVO (BRVO) is typically located at an arteriovenous crossing, and the occlusion causes tortuous dilated vessels, flame-shaped haemorrhages, cotton-wool spots and ischaemia in the area upstream of the affected vein. Macular oedema is the primary cause of vision loss in BRVO. For decades, the treatment of macular oedema in BRVO was central retinal laser photocoagulation based on results from the Branch Vein Occlusion Study (BVOS) Group. They included BRVO and hemiretinal RVO (HRVO) patients and found 65% of treated eyes to improve two or more lines of vision, compared with 37% of untreated eyes (BVOS Group 1984). However, the detrimental effect of laser is an ongoing subject of concern, and the treatment was largely replaced by intravitreal treatment injections with steroids or vascular endothelial growth factor (VEGF) inhibitors, when these were introduced in Europe in 2010 and 2011 (EMA 2010; EMA 2011).

Vascular endothelial growth factor inhibitory agents have consistently demonstrated high efficacy and safety in patients with macular oedema due to BRVO (Campochiaro et al. 2010; Campochiaro et al. 2015). Important drawbacks to anti-VEGF are the need for frequent re-treatments, which urges the development of new treatment regimens to lower treatment need. However, most previous attempts to study combination treatment have not been able to demonstrate any such effect (Tadayoni et al. 2017; Callizo et al. 2019). In fact, only one study in BRVO patients found a lower need for re-treatment when adding laser photocoagulation (Donati et al. 2012).

The navigated laser delivery system allows for safe and precise application of macular grid laser treatment, and a study in patients with diabetic macular oedema (DMO), demonstrated significantly lower re-treatment need when applying navigated laser in combination with anti-VEGF (Liegl et al. 2014). No previous studies have evaluated the effect of navigated central laser on re-treatment need in BRVO patients.

In this randomized study of treatment-naïve patients with BRVO and macular oedema, we aimed to compare aflibercept and navigated laser versus aflibercept monotherapy in order to evaluate if the addition of navigated laser would reduce the treatment burden while maintaining functional and anatomical efficacy within the first 12 months of treatment, and if navigated laser treatment affected retinal sensitivity measured by microperimetry.

Methods

In a randomized controlled open-label design, study participants were included from the Departments of Ophthalmology at Odense University Hospital, Odense, Denmark and Zealand University Hospital, Roskilde, Denmark. Eligibility criteria were as follows: any active retinal or iris neovascularization in the study eye, cataract, vitreous haemorrhage, or other clouding conditions that would prevent retinal laser photocoagulation, macular oedema and/or increased retinal thickness due to other potential causes than BRVO. Patients not suitable for laser at month three were re-evaluated for laser eligibility at month four and five. If patients were still unsuitable at month five, laser was not applied, and patients continued monthly examinations in their appointed treatment group.

All participants were examined monthly from month 4 through 12 by BCVA, intraocular pressure and OCT and re-treated with aflibercept according to re-treatment criteria: increase in CRT ≥20% compared with the lowest measurement, or decrease in BCVA >5 ETDRS letters as compared to baseline. Furthermore, participants were re-examined by FFA and microperimetry at month 12.

Central retinal laser photocoagulation

Navigated central retinal laser photocoagulation was planned according to the BVOS study and the ETDRS protocol (BVOS Group 1984; ETDRS 1985; ETDRS 1987), but modified to apply less intense, lighter burns.

Treatment targeted areas of non-perfusion, diffuse leakage and leaking microaneurysms within the vascular arcades. A new FFA was performed...
prior to the laser treatment session. This was imported into the Navilas® software, overlayed onto the fundus photograph captured by the Navilas® fundus camera, and used for preplanning the treatment session. Treatment was performed without use of contact lens, if possible, and the build-in automated eye tracking and image stabilization were utilized during application of laser burns. Spot size was 100 µm with a pulse duration of 20 ms for grid treatment and 100 ms for focal treatment (leaking microaneurysms). Burns were at least one burn widths apart, with longer distance in case of large area of treatment. Power was titrated, starting from 70 mW, to achieve barely visible whitening of the retina. For focal treatment of microaneurysms, power was titrated until mild whitening beneath the microaneurysm, but not necessarily any colour change in the microaneurysm itself.

 Rescue laser of the affected peripheral retinal sector was allowed in case of incident neovascularizations during follow-up.

Data on number of spots, power, pulse duration, spot size and total applied power were collected.

**Microperimetry**

Microperimetry was performed on both eyes separately. The pattern of stimuli contained 45 points, organized in a circular pattern in the central 12 degrees of the macula, centred over the fovea. The fixation target was a 0.5 degree red circle which could be increased in size if needed. The size of the stimuli was Goldmann III, colour was white and duration was 200 ms with a stimulation staircase strategy of 4-2-1. Starting threshold at the baseline examination was set to 12 dB for one initial test point in each quadrant. The apparatus performed automatic retinal focusing and automatic alignment of the pupil and retina. Analysis was automatically paused during significant eye movements. At the end of examination, a fundus photograph was acquired and aligned with the infrared image for the correct position. At month 12, follow-up function was utilized ensuring the same starting threshold and anatomic location of each test point as at baseline. The threshold of all 45 test points was averaged and presented as mean retinal sensitivity. A mean retinal sensitivity change from baseline to month 12 was calculated.

**Statistical analysis**

Characterization of participants on demographics and baseline variables as well as outcome parameters were presented as counts and proportions with 95% confidence intervals (CI) for categorical variables and mean ± SD or median and quartiles (25%, 75% percentile) for continuous variables as appropriate. An evaluation was done using chi-squared test or Fisher’s exact test for categorical variables and Student’s t-test or Wilcoxon rank-sum test for continuous variables as appropriate.

The primary outcome was percentage of patients needing re-treatment after aflibercept loading phase. The sample size was based on a power calculation utilizing a statistical significance level of 0.05 (α), a power of 0.90 and test statistics were proportions (p1 = 0.65 and p2 = 0.16), which estimate a minimum of 19 patients in each treatment group. Proportions were estimated for primary outcome only, and was based on the study by Liegl et al. (2014).

Secondary outcomes include number of injections after loading phase, mean BCVA, median CRT and mean retinal sensitivity at month 12, change in BCVA and CRT from baseline through month 12, number of patients improving more than 10 ETDRS letters, ratio of patients without oedema (defined as CRT < 300 µm) at month 12 and change in central retinal sensitivity. Of these, mean BCVA, median CRT and mean retinal sensitivity at month 12 as well as change in CRT and number of patients improving more than 10 ETDRS letters were added after the study commenced to improve comparability with previous studies.

Change in BCVA between baseline and month 12 was tested by applying a mixed-model analysis with a difference in BCVA from baseline as an outcome variable and adjusting for baseline BCVA (continuous), visit number (categorical), and an interaction term of visit number and randomization group to account for the fact that effect of randomization may not be equal over visits. Change in CRT was tested by applying a similar model. The number of injections after the loading phase and the number of patients improving more than 10 ETDRS letters were tested by applying a Poisson regression model with randomization variable as predictor. Change in retinal sensitivity was tested by Wilcoxon rank-sum test and subsequently evaluated by applying a linear regression model, adjusting for baseline retinal sensitivity.

All analyses were performed as intention-to-treat analyses. A secondary per-protocol analysis was performed, with no major differences in results (data available on request).

**Ethics**

The study was carried out according to the Tenets of the Declaration of Helsinki. All participants provided written informed consent prior to study inclusion. The study was approved by the Regional Scientific Ethical Committee of Southern Denmark (S-201700084) and registered at ClinicalTrials.gov prior to initiation (NCT03651011).

**Results**

Forty-five eyes of 45 patients were included between August 2018 and August 2020. Two patients dropped out of each treatment group (two due to the COVID-19 pandemic, one due to sudden critical illness and one due to patients wish), leaving 41 patients with complete follow-up (Fig. 1 for complete flowchart of inclusion). Of these, 22 were included at Odense University Hospital, Odense, Denmark, and 19 at Zealand University Hospital, Roskilde, Denmark. Patients that dropped out did not differ in baseline characteristics compared to the overall cohort (data not shown). Two patients in Group A were unsuitable for laser at month three through five (one due to refractory intraretinal haemorrhage and one due to absence of target for treatment, that is, no visible nonperfusion, diffuse leakage or leaking microaneurysms on fluorescein angiography) and did not receive laser treatment. Five patients received laser treatment between month 4 and 5, with treatment initially postponed due to refractory intraretinal haemorrhage (three) or refractory oedema (two). Thus, laser treatment was performed in 19 of 21 patients, with no use of contact lens necessary at
Fig. 1. Flowchart of patient inclusion in the study.

Discussion

In this randomized clinical study, comparing combination treatment with navigated central retinal laser treatment and aflibercept against aflibercept alone for BRVO with macular oedema, the addition of laser did not affect the need of intravitreal therapy, nor the functional or anatomical outcome of the treatment.

The effect of aflibercept in treatment of macular oedema in BRVO was well-established in the VIBRANT trial, finding a significant effect on structural and functional outcomes (Clark et al. 2016). Similar effects have been demonstrated for other VEGF inhibitory treatments (Campochiaro et al. 2010; Hikichi et al. 2014). The effect of laser treatment is also well documented, though inferior to anti-

Table 1. Baseline characteristics of all participants and separate according to treatment group

<table>
<thead>
<tr>
<th></th>
<th>Group A (Navilas laser) (n = 21)</th>
<th>Group B (No laser) (n = 20)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female (%)</td>
<td>13 (62%)</td>
<td>10 (50%)</td>
<td>23 (56%)</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>69.4 (11.3)</td>
<td>66.7 (8.7)</td>
<td>69.6 (10.0)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m² (SD)</td>
<td>27.4 (4.2)</td>
<td>27.0 (4.8)</td>
<td>27.2 (4.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg (SD)</td>
<td>154 (23)</td>
<td>154 (23)</td>
<td>154 (23)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg (SD)</td>
<td>95 (15)</td>
<td>91 (11)</td>
<td>93 (14)</td>
</tr>
<tr>
<td>Smoking, cigarette pack-years (25;75 percentile)</td>
<td>15.0 (1.0;25.0)</td>
<td>0.5 (0.0;13.0)</td>
<td>10.0 (0.0;23.0)</td>
</tr>
<tr>
<td>BCVA, ETDRS letters (25;75 percentile)</td>
<td>73.0 (64.0;76.0)</td>
<td>68.0 (60.5;72.5)</td>
<td>70.0 (62.0;75.0)</td>
</tr>
<tr>
<td>Central retinal thickness, μm (25;75 percentile)</td>
<td>505 (446;581)</td>
<td>494 (454;504)</td>
<td>502 (449;580)</td>
</tr>
<tr>
<td>Mean retinal sensitivity, dB (SD)</td>
<td>21.9 (4.1)</td>
<td>20.7 (3.9)</td>
<td>21.3 (4.0)</td>
</tr>
</tbody>
</table>

Categorical data presented as count (%) and continuous data presented as mean (SD) or median (25;75 percentile) as appropriate. BCVA = Best Corrected Visual Acuity, ETDRS = Early Treatment Diabetic Retinopathy Study.
VEGF treatment (Branch Vein Occlusion Study Group 1984; Tadayoni et al. 2017). In theory, combination treatment would unify the prolonged effect of retinal photocoagulation with the superior outcomes of VEGF inhibitory treatment, but we did not detect any advantages of combination treatment in our study. Re-treatment need was similar between groups indicating that there is either no effect of adding navigated central laser photocoagulation, or the difference is too little to demonstrate in a study of this size and follow-up time.

Overall, we report a lower than expected re-treatment need in both treatment arms, equal to or below two injections after the loading phase, and five injections during complete follow-up, under the given re-treatment criteria. In comparison, the VIBRANT study reports aflibercept-treated eyes to receive an obligatory six injections in the first 20 weeks of treatment, and a mean of nine injections over the complete 48 weeks of the study, and

### Table 2. Need for re-treatment of intravitreal VEGF inhibition, change in BCVA, CRT and retinal sensitivity from baseline through month 12 according to treatment group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of eyes receiving re-treatment (M4-M12), n (% [95% CI])</th>
<th>Median no. of anti-VEGF injections (M4-M12) (25;75 percentile)</th>
<th>Mean BCVA at M12, ETDRS letters (SD)</th>
<th>Mean change in BCVA at M12, ETDRS letters (SD)</th>
<th>No. of patients improving more than 10 ETDRS letters, n (% [95% CI])</th>
<th>Median CRT at M12, µm (25;75 percentile)</th>
<th>Change in CRT (M0-M12), µm (25;75 percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (Navilas laser; n = 21)</td>
<td>15 (71% [49;87%])</td>
<td>1 (0.3)</td>
<td>80.7 (10.9)</td>
<td>12.8 (9.4)</td>
<td>13 (62% [40;80%])</td>
<td>289 (287;306)</td>
<td>−195 (−276;−145)</td>
</tr>
<tr>
<td>Group B (No laser; n = 20)</td>
<td>16 (80% [56;93%])</td>
<td>2 (1;5)</td>
<td>80.5 (9.1)</td>
<td>15.1 (9.6)</td>
<td>14 (70% [47;86%])</td>
<td>294 (269;311)</td>
<td>−181 (−263;−157)</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.72</td>
<td>0.43</td>
<td>0.95</td>
<td>0.48</td>
<td>0.74</td>
<td>0.82</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Categorical data presented as count (% [95% CI]) and continuous data presented as mean (SD) or median (25;75 percentile) as appropriate. Change in BCVA and CRT represents unadjusted mean/median change, while p-value reflects a mixed model analysis of change adjusted for baseline value, visit number, and the interaction of visit number and randomization group. Full model outputs are available on request.

CI = Confidence interval, BCVA = Best Corrected Visual Acuity, CRT = Central Retinal Thickness, ETDRS = Early Treatment Diabetic Retinopathy Study, M0 = Month 0, M12 = Month 12, M4 = Month 4, M7 = Month 7, VEGF = Vascular Endothelial Growth Factor.

**Fig. 2.** Mean and median change ±95% CI of best-corrected visual acuity (BCVA) to the left and central retinal thickness (CRT) to the right from baseline/month 0 to month 12 according to treatment group. CI = Confidence Interval, ETDRS = Early Treatment Diabetic Retinopathy Study.
achieved comparable anatomical and functional outcomes. Thus, our treatment regimen is efficient, independently of treatment group, utilizing a low number of injections.

Direct comparison of laser treatment studies is complicated by different laser treatment regimen, where treatment focus, timing and planning varies widely. Using navigated laser in combination treatment, Liegl et al. (2014) evaluated 66 patients with centre-involving DMO and found a significantly lower need of injections in the combination treatment group. The treatment regimen and re-treatment criteria were comparable to ours and follow-up time was the same. But the study differed from ours in evaluating a different basic disease as ground for macular oedema, utilizing ranibizumab as VEGF inhibitory treatment, applying laser with a slightly different treatment protocol differing primarily in pulse duration, and their patients had significantly lower baseline visual acuity (24.6–30.8 ETDRS letters versus our 68.0–73.0 ETDRS letters), which might attribute to differences in results.

Another study provided a head-to-head comparison of combination treatment with navigated versus conventional laser in DMO. They found no difference between groups, and concluded that the timing of laser after anti-VEGF loading might be attributable to the good outcomes (Blindbæk et al. 2020). This is supported by a combination treatment study in BRVO, that apply laser shortly after VEGF inhibitory treatment and find lower re-treatment need in the laser treatment group (Donati et al. 2012). However, a few studies also evaluated similar regimens in BRVO, without any difference in treatment burden between groups (Tadayoni et al. 2017; Callizo et al. 2019).

Within aflibercept studies in BRVO, different re-treatment regimens without the application of laser photocoagulation have been evaluated (Treat and extend, treat and monitor), finding low re-treatment need with good functional and anatomical results (Pichi et al. 2019; Arai et al. 2020; Park et al. 2021). Some studies even find just one loading dose, followed by as-needed treatment, enough to maintain good treatment outcomes (Pichi et al. 2019; Sakinashi et al. 2021). A knowledge gap remains, since no studies provide a head-to-head comparison of treat-and-extend versus as-needed regimens or number of loading doses in BRVO.

When comparing structural outcomes in the studies, one must be aware of the risk of a ceiling effect due to large differences in baseline measures. For example, studies evaluating combination treatment of anti-VEGF and laser photocoagulation report baseline BCVA values ranging from 42.9 to 59.5 letters, all considerably lower than our mean baseline BCVA of 70.0. (Stenner et al. 2020). Despite of this, we demonstrate similar increases in BCVA, with a similar number of re-treatments.

We argue, based on the results of this study, that an as-needed regimen after loading of aflibercept, is effective in the treatment of BRVO with macular oedema, with a low VEGF-inhibitory treatment burden and that the addition of laser cannot be demonstrated to be the decisive factor. Whether the addition of laser, may be beneficial in a selected patient group, that is patients with more severe disease at baseline, anti-VEGF refractory oedema, or low compliance, is a subject of further investigation.

In microperimetry measurement, though statistically insignificant, a slight numerical difference in change in mean retinal sensitivity between treatment groups was demonstrated. This could indicate a subclinical detrimental effect of laser treatment on retinal sensitivity. However, we subsequently evaluated only the affected half of the macula, and since a slight numerical difference in mean sensitivity between groups existed at baseline, we adjusted for the baseline retinal sensitivity which evened out any numerical differences (data not shown). When also accounting for the increased test-retest variability in eyes with macular diseases, laser treatment did not affect retinal sensitivity in our study (Palkovits et al. 2018).

Our study was strengthened by the prospective, randomized, controlled design and was, to our knowledge, the first study to evaluate navigated central retinal laser treatment in combination with anti-VEGF for BRVO patients. It does, however, include limitations. First, the study includes a relatively low number of patients, though sample size was grounded in a power calculation based on the results from a previous study in DMO, as enough to demonstrate a similar difference in treatment results of BRVO patients. While we acknowledge that a study in DMO patients might differ from a study in BRVO patients, this was considered the best possible basis for at power calculation, since no similar studies existed in BRVO. Second, although the criteria for re-treatment were based on earlier study protocols, is it not possible to rule out that conducting the study with a lower threshold for re-treatment might have led to other results. Given the fact that postoperative improvements in BCVA compared well with previous studies, we do not, however, expect that patients were treated insufficiently.

Third, the Danish nationwide lockdown due to the COVID-19 pandemic resulted in a few withdrawal of consent and rescheduling of patient visits, thus, follow-up time differed slightly from protocol.

Conclusion/perspectives

Navigated central laser in combination with aflibercept is not associated with a lower need for re-treatment than aflibercept monotherapy in the treatment of macular oedema due to BRVO. Combination treatment was equal to anti-VEGF monotherapy in functional and structural outcomes, and was safe with regard to retinal sensitivity, evaluated by microperimetry.

References


