Aflibercept and navigated versus conventional laser in diabetic macular edema: a 12-month randomized clinical trial

Søren L Blindbæk, MD1, 2, 3, Tunde Peto, PhD2, 4, Jakob Grauslund, DMSci1, 2, 5

1 Department of Ophthalmology, Odense University Hospital, Odense, Denmark
2 Department of Clinical Research, University of Southern Denmark, Odense, Denmark
3 OPEN, Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark
4 Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom.
5 Steno Diabetes Center Odense, Odense, Denmark

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Corresponding author:
Søren Leer Blindbæk
Department of Ophthalmology, Odense University Hospital, Odense, Denmark
Sdr. Boulevard 29, Odense C – DK-5000
Phone: +45 2179 4056
E-mail: Soeren.leer.blindbaek@rsyd.dk
Fax: +45 6612 3468
Abstract

Purpose: To examine the efficacy of intravitreal aflibercept and navigated laser as compared to intravitreal aflibercept and conventional laser in diabetic macular edema (DME) treatment.

Methods: In 12-month randomized clinical trial forty-eight eyes of 37 patients with centre-involved DME at Odense University Hospital were randomized 1:1 to receive three monthly injections of aflibercept followed by navigated (group A) or conventional (group B) focal/grid laser. From month four through twelve, patients were examined monthly, and additional injections were given pro re nata (PRN) (central retinal thickness [CRT] > 20% from lowest measurement or loss in visual acuity [VA] > 5 Early Treatment Diabetic Retinopathy Study [ETDRS] letters compared to baseline). Outcome measures; 1) percentage of eyes that needed additional injections after laser in group A and B, 2) mean number of injections in group A and B, and 3) mean change in VA and CRT in group A and B.

Results: In the PRN-phase, 60.5% of patients needed additional injections without differences between groups A and B (58.3 vs 63.2%, p>0.99). The mean number of injections between baseline and month 12 was 4.4 (4.2 vs 4.6, p=0.41). From baseline to month 12, VA improved by 8.4 ETDRS letters, and CRT was reduced by 97.4 µm (+9.4 vs +7.1 letters, p=0.17, and -83.2 vs -115.4 µm, p=0.21).

Conclusion: No difference in need for re-treatment was detected between treatment arms of aflibercept and navigated vs conventional laser. Good functional outcome was demonstrated with a mean of only 4.4 intravitreal injections during the first year of therapy.

Keywords: diabetic macular edema, anti-VEGF, focal/grid laser photocoagulation, randomized clinical trial
Introduction

Diabetic macular edema (DME) is a leading cause of visual impairment in the working aged population in developed countries (Klein et al. 2009). It was established by the Early Treatment Diabetic Retinopathy Study (ETDRS) that focal/grid laser photocoagulation reduces the risk of visual loss in patients with centre involving DME but with a small likelihood of visual improvement (Early Treatment Diabetic Retinopathy Study Research Group 1991). Currently, vascular endothelial growth factor (VEGF) inhibitors are the established first line of treatment and have consistently demonstrated efficacy in DME-treatment (Massin et al. 2010; Do et al. 2012; Nguyen et al. 2012; Brown et al. 2015; Wells et al. 2016). However, a high number of injections are needed to sustain visual improvement (Elman et al. 2010).

Whereas the efficacy of focal/grid laser photocoagulation is modest in regards of visual improvement, its protracted effect is a desired shortcoming of current anti-VEGF agents. Hence, combination therapy could be attractive to relieve the burden of repetitive intravitreal injections. However, most attempts with combination therapy for DME have so far not been able to reduce the need of intravitreal therapy. For instance, the DRCR.net Protocol I trial demonstrated a need of nine injections during the first year of treatment without differences between treatment arms of mono- and combination therapy. Similar results with a need of seven, eight and ten injections were demonstrated in the RESTORE, REVEAL and TREX-DME studies, respectively (Elman et al. 2010; Mitchell et al. 2011; Ishibashi et al. 2015; Payne et al. 2017).

Modern navigated laser photocoagulation systems benefit from technical advantages of integrated software which allows for capture and/or import and overlay of e.g. fundus fluorescein angiography (FFA) images and optical coherence tomography (OCT) thickness maps. Focal treatment of leaking microaneurysms or grid treatment in areas of diffuse edema is pre-planned and, as compared to conventional focal/grid laser photocoagulation, image stabilization and tracking is used to apply laser burns with increased precision and with a lower need for retreatment (Kernt et al. 2012; Neubauer et al. 2013).

In a 12-month prospective study of patients with centre-involving DME, Liegl et al. compared navigated focal/grid laser photocoagulation and ranibizumab with ranibizumab monotherapy (Liegl et al. 2014). In three years of treatment the study demonstrated a similar improvement in best-corrected visual acuity (BCVA) but with a lower need for additional intravitreal injections in the combination group (Herold et al. 2018). However, it is unknown whether the difference in results of combination therapy in DME-treatment can be attributed to the choice of photocoagulation system.

Materials and methods

We conducted a 12-month prospective randomized clinical trial including 48 eyes of patients with centre involving DME referred to Odense University Hospital, Denmark, between 1 October 2015 and 31 December 2017.
Criteria of eligibility were DME, age 18-99 years, BCVA between 35 and 80 ETDRS letters, and CRT of more than 300 µm in the study eye. We excluded patients who were pregnant, had active proliferative diabetic retinopathy, a history of intraocular surgery or retinal photocoagulation within four months prior to inclusion or ocular condition(s) in the study eye that in the opinion of the investigator would prevent improvement of visual acuity.

A full medical history was obtained at baseline; examination included BCVA, slit lamp examination and fundus bio microscopy in mydriasis with tropicamide 10 mg/mL and phenylephrine 10 %, optical coherence tomography (OCT) by 3D OCT-2000 Spectral domain OCT (Topcon, Tokyo, Japan) and 50 degrees, macula-centred FFA (TRC-50DX fundus camera, Topcon, Tokyo, Japan). BCVA was assessed using ETDRS charts (Precision Vision, Illinois, USA) at a starting distance of four meters. Furthermore, brachial arterial blood pressure (Omron 705CP, Hoofdrop, The Netherlands) and haemoglobin A1c (HbA1c) (Tosoh G8, Alere, Holstebro, Denmark) were measured. Body mass index (BMI) was calculated, and smoking was quantified as pack-years. One pack year was defined as 20 cigarettes/day for one year.

All patients then received three monthly intravitreal injections of 2.0 mg aflibercept. BCVA, OCT and FFA were repeated four weeks after the last injection (month 3) and angiography guided focal/grid laser photocoagulation was performed using either Navilas®(OD-OS GmbH, Teltow, Germany) (group A) or PASCAL® laser (Optomedica Corp., Santa Clara, CA, USA) (group B) at 24-48 hours after dye injection. Automated randomization to either group A or B was done at baseline by an algorithm unknown to the investigators before the first injection of aflibercept. If both eyes of the same patient were eligible for inclusion the right eye or the eye with primary debut was randomized and the second eye was allocated to the opposite treatment arm (Armstrong 2013).

From month four through month twelve, patients were examined monthly and additional intravitreal injections were given pro re nata (PRN). Criteria for re-treatment were CRT > 20% from lowest measurement or loss in BCVA > 5 ETDRS letters as compared to baseline. Eyes not suitable for laser at month three as determined by the investigator continued in the PRN intravitreal regimen. If laser had not been given by the end of month five patients were withdrawn from the study.

**Focal/grid laser photocoagulation**

In both treatment arms, focal/grid laser photocoagulation was given according to a modified ETDRS protocol. The modified protocol primarily differed from the original focal/grid laser protocol described by the ETDRS in applying lighter and less intense burns (Early Treatment Diabetic Retinopathy Study Research Group 1985; Early Treatment Diabetic Retinopathy Study Research Group 1987). Treatment targeted leaking microaneurysms, areas of diffuse leakage, and areas of non-perfusion.

Both navigated and conventional laser was guided by FFA performed at month three. For navigated laser, FFA was imported to the Navilas® software, and treatment was preplanned using image overlay with a fundus photo captured by the Navilas® fundus camera. Automated tracking and image stabilization was used to apply laser burns. If possible, treatment was carried out without the use of a contact lens. For conventional focal/grid laser photocoagulation, FFA was displayed on a monitor visible to the clinician during treatment, and a Mainster Focal/Grid lens with an image magnification of x 0.96 was used.
Both focal and grid treatment were carried out with a spot size of 100 µm. Pulse duration was set at 100 ms for focal treatment of leaking microaneurysms and 20 ms for grid treatment. Burns were placed at least one spot width apart and power was titrated to achieve barely visible whitening. Treatment of microaneurysms did not require a treatment-induced change in microaneurysm colour but at least a mild grey-white burn should be evident beneath all treated microaneurysms.

**Statistical analysis**

All statistical calculations were performed using STATA version 15.1 (StataCorp LLC, College Station, TX, USA). Continuous data are presented as mean (with 95% confidence intervals) and categorical data as percentages. Probabilities of 0.05 or less were interpreted as indicating statistically significant differences in outcome. Comparisons between groups were tested employing cluster robust standard errors for linear regression models, as patients were allowed to participate with both eyes. Fisher’s exact test was used for comparison of proportions. Sample size was determined by a calculation of power comparing proportions of two independent samples that stated a required inclusion of minimum 19 eyes in each group (α=0.05, power=0.90, p1=0.65, p2=0.16 and n2/n1=1). Proportions (p1 and p2) were determined for the primary outcome (percentage of eyes that needed additional aflibercept injections after laser in group A and B) based on the results presented by Liegl et al. (Liegl et al. 2014). To compensate for an estimated drop-out of 20% during follow-up, we aimed to include 24 eyes in each group.

**Ethical aspects**

This study was carried out in accordance with the tenets of the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. Ethical approval was obtained from the Regional Scientific Ethical Committee for Southern Denmark and the trial was registered at http://www.clinicaltrials.gov before initiation (NCT02554747).

**Results**

Forty eight eyes of 37 patients fulfilled the criteria of inclusion. One patient died during follow-up of reasons not related to the study. One was excluded as the patient was unable to follow scheduled study visits while hospitalized for severe complications to diabetes. In addition, three patients were excluded according to protocol at month five as their eyes were not suitable for focal/grid laser photocoagulation (Fig. 1).

This led to a final inclusion of 43 eyes of 32 patients. Eleven were women (14 eyes) and 21 were men (29 eyes). Thirty had type 2 diabetes and two had type 1 diabetes; mean HbA1c was 61.7 mmol/mol. Mean age and duration of diabetes were 63.5 and 12.6 years, respectively and mean systolic and diastolic blood pressure was 140.8 and 81.5 mmHg. Mean BMI was 29.4 kg/m², and the mean number of pack-years was 15.0. Thirteen eyes had previously been subjected to intraocular surgery (intravitreal VEGF inhibition: 3, focal/grid laser photocoagulation: 6, cataract extraction: 12, posterior capsulotomy: 5, panretinal photocoagulation: 4 and vitrectomy: 1). Mean BCVA was 71.1 ETDRS letters, and mean CRT was 387.5 µm.
An overview of baseline characteristics for all included patients and patients in group A and B separately is presented in Table 1. No imbalances between groups were detected.

**Table 1**

Between baseline and follow-up at month 12, BCVA improved by 8.4 ETDRS letters with no statistically significant differences between eyes in group A and B (+9.4 and +7.1, p=0.17). Likewise, there was a CRT-reduction of 97.4 µm with no difference between group A and B (-83.2 µm and -115.4 µm, p=0.21).

The percentage of eyes with an improvement in letter score of 10 or more was 39.5 (17/43) and 16.3% (7/43) gained 15 letters or more from baseline to month 12.

The mean number of intravitreal aflibercept injections from baseline through month 12 was 4.4 (3.9-4.8) and similar in groups A and B (p=0.41). Overall, 60.5% (26/43) of patients needed further treatment after focal/grid laser photocoagulation (58.3% and 63.2% in groups A and B, p>0.99) (Table 2).

**Table 2**

In a secondary analysis including 36 treatment naïve eyes (18 eyes from groups A and B, respectively) of 26 patients (excluding patients that had previously undergone vitrectomy, PRP, focal/grid laser photocoagulation or intravitreal VEGF inhibition), mean BCVA-improvement was 9.3 (7.4-11.2) ETDRS letters, and mean CRT reduction was -96.7 (-64.9-(-128.4)) µm between baseline and follow-up. The mean number of injections needed from baseline through month twelve was 4.3 (3.8-4.7), and 63.6% of patients needed further anti-VEGF treatment after focal/grid laser photocoagulation.

**Discussion**

In a randomized clinical trial comparing the efficacy of navigated versus conventional focal/grid laser photocoagulation in addition to intravitreal aflibercept in DME, no differences were detected between treatment arms in regards of need for re-treatment, VA or retinal thickness. However, this study demonstrated that regardless of laser regimen, functional and anatomical success was achieved in most eyes with only 4.4 intravitreal injections within 12 months. Furthermore, introduction of focal/grid laser photocoagulation treatment after intravitreal loading with three monthly injections halted further need of treatment in approximately forty per cent of eyes.

With similar improvement in BCVA, the need for intravitreal therapy was considerably lower in our study in comparison with previous studies of intravitreal agents in either monthly, PRN or treat and extend regimens (Blindbaek et al. 2018). In the majority of previous studies with anti-VEGF for DME, one of two overall approaches for laser administration has been applied. One is prompt laser administered either prior to VEGF inhibition or within the first few days after the first injection. In the DRCR.net Protocol I trial (ranibizumab + prompt laser arm) and the RESTORE and REVEAL studies, no additional benefits of combination therapy were demonstrated as compared to anti-VEGF monotherapy (Elman et al. 2010; Mitchell et al. 2011; Ishibashi et al. 2015).

The other approach have been deferred/rescue focal/grid laser photocoagulation, usually not permitted until week 24, reserved for those who do not respond satisfactory to anti-VEGF.
monotherapy. This method has been applied in the DCRR.net Protocol I trial (ranibizumab + deferred laser arm) and T, VIVID/VISTA, RESOLVE and DA VINCI (Elman et al. 2010; Massin et al. 2010; Do et al. 2012; Korobelnik et al. 2014; Wells et al. 2015). As for the studies with prompt laser, no additional benefits of combination therapy were demonstrated over anti-VEGF monotherapy.

In this present study as well as in the study by Liegl et al. (combination therapy arm), focal/grid laser photocoagulation was applied after a loading dose of three monthly anti-VEGF injections. Both studies successfully demonstrated a lower need for intravitreal therapy with similar improvement in visual acuity (Liegl et al. 2014). Likewise, recently published data demonstrated similar results with combination therapy applying micropulsed yellow laser following the same treatment algorithm (Khattab et al. 2019). Our results, with similar efficacy irrespective the choice of laser system, thus indicate that differences in results should rather be attributed to treatment algorithms and laser timing than to the choice of laser system.

The mechanistic effects of focal/grid laser photocoagulation are not fully understood. Hence, it is hard to explain differences in effect size depending on the approach to focal/grid laser photocoagulation. It has been proposed that retinal laser reduces VEGF expression and decreases hydrostatic pressure due to a reduced metabolic demand of the remaining retinal tissue and increased oxygen flux from the choroid through laser scars (Gottfredsdottir et al. 1993; Aiello et al. 1994; Augustin et al. 2001; Nguyen et al. 2004; Stefansson 2006). We speculate that a more uniform burn intensity and controlled extend of treatment can be achieved once CRT is reduced prior to focal/grid laser photocoagulation as compared to prompt delivery of laser with untreated edema or considerable residual edema once only a single anti-VEGF has been administered. Whether this influences the effects of treatment is, however, unknown. In regards of rescue laser, comparison seems less reasonable as focal/grid laser photocoagulation is reserved for those with an already unsatisfactory response to anti-VEGF treatment. Furthermore, the number of anti-VEGF injections prior to laser as well as intervals between anti-VEGF and laser treatment will be less uniform as compared to this present study.

Comparison of functional outcome between studies is complicated due to considerable differences in baseline BCVA and hence the risk of a ceiling effect. E.g. mean BCVA at baseline was approximately 60 and 64 ETDRS letters in the VIVID/VISTA trials and the DCRR.net Protocol T, respectively, as compared to 71 ETDRS letters in this present study (Korobelnik et al. 2014; Wells et al. 2015). However, estimated efficacy in our study was comparable to other trials with anti-VEGF for DME in regards of VA improvement (Blindbaek et al. 2018). Furthermore, the percentages of eyes with an improvement in letter score of 10 or more and 15 or more in our study were 40 and 16, respectively. This is comparable to the results of the DCRR.net Protocol T trial in which the corresponding percentages were 50 and 18 in the aflibercept arm of patients with a baseline BCVA between 69 and 78 ETDRS letters (mean 73.5±2.6). However, the results of our study were achieved with the use of only four intravitreal injections during the first year of treatment.

A numerically greater proportion of eyes experienced VA improvement of more than 10 ETDRS letters in the navigated laser arm. However, our study was not powered to detect differences in VA improvement and any potential true difference did, thus, not reach statistical significance.

Approximately one-third of the eyes included in this study were fellow-eyes. To account for any interpatient correlation the first eye was randomized to treatment arm whereas fellow-eyes were allocated to
the opposite treatment arm and differences between groups were tested employing cluster robust standard errors for linear regression models. This method allows fellow-eyes to be included to increase power as one eye acts as control for the other and ensures that right and left eyes are randomly allocated to either treatment arm (Armstrong 2013).

This study was strengthened by the prospective, randomized design and was the first to conduct a head-to-head comparison of modern navigated laser (Navilas®) and conventional slit-lamp based laser (Pascal) in combination therapy for DME.

A limitation to the study was the number of participants. However, any clinically meaningful differences between treatment arms were predefined and sample size was calculated based on results from previous studies of similar design. Thus, conclusions based on results of this study are presented with the desired strength and magnitude even though a larger sample size would of course be preferable. In addition, the design of this study could have been strengthened further by inclusion of a control group treated with aflibercept alone, which was, however, not the primary aim of this study.

In conclusion, no differences were demonstrated in regards of need for re-treatment or functional outcome between treatment arms of aflibercept and navigated vs. conventional focal/grid laser photocoagulation in DME. Furthermore, this study demonstrated a good functional outcome, but a considerably lower need for intravitreal aflibercept, in patients with centre-involved DME as compared to previous studies with aflibercept monotherapy. Our results suggest that with proper timing of focal/grid laser photocoagulation combination therapy may reduce the need for intravitreal therapy during the first year of treatment.

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**Fig. 1** Patient flowchart illustrating recruitment and randomization process. *DME: diabetic macular edema.* Group A: Aflibercept + navigated focal/grid laser photocoagulation (Navilas). Group B: Aflibercept + conventional focal/grid laser photocoagulation (Pascal).