Functional and structural efficacy of a novel combinational therapy of aflibercept and timely focal/grid photocoagulation in diabetic macular oedema: do clinical study results compare favourably with a standard-of-care treated real-world population?

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ABSTRACT.

Purpose: To evaluate treatment efficacy in diabetic macular oedema (DME) comparing a study population receiving combined intravitreal vascular endothelial growth factor (VEGF) inhibition and focal/grid photocoagulation with a matched, real-world population receiving standard of care treatment.

Methods: In an exploratory study, we included 43 eyes from 32 patients from a previously published study as well as 46 eyes from 38 standard-of-care patients. The study population had received a loading dose of three monthly aflibercept injections followed by focal/grid photocoagulation and additional aflibercept *pro re nata*. Principal measurements at 12 months were numbers of intravitreal injections, best corrected visual acuity (BCVA) and central retinal thickness (CRT).

Results: At baseline, there were no differences between groups regarding age, sex, body mass index, haemoglobin A_1C, systolic pressure or type of diabetes, but the study population had a higher diastolic pressure (81.6 versus 72.1 mmHg, p = 0.03) and a lower duration of diabetes (12.3 versus 23.2 years, p = 0.03). At month 12, patients in the study group had a higher visual acuity (79.6 versus 74.3 ETDRS letters, p = 0.03), despite having received fewer aflibercept injections (4.4 versus 5.9, p < 0.01) with a higher likelihood of having only received the three mandatory injections in the loading phase (39.5% versus 13.0%, p = 0.01).

Conclusion: In comparison to a matched, real-world DME-population, patients in combined treatment with intravitreal aflibercept and postloading focal/grid photocoagulation obtained a better functional outcome despite having received fewer intravitreal injections. Future randomized studies are needed to evaluate the long-term efficacy of this combined treatment regimen.

Introduction

Almost half a billion people worldwide suffer from diabetes, a number estimated to increase with 25% by the year of 2030 (Saeedi et al. 2019). As more than one third of these patients have diabetic retinopathy (DR), it is a major complication to diabetes, which untreated can lead to blindness (Cohen & Gardner 2016). An advanced manifestation of DR is diabetic macular oedema (DME) (Johnson 2009), which is characterized by retinal thickening caused by accumulation of macular fluid (Musat et al. 2015). As chronic hyperglycaemia causes oxidative stress in the retina, an upregulation of vascular endothelial growth factor (VEGF) is induced, contributing to endothelial cell proliferation, vasodilation, inflammation and increase in vascular permeability leading to breakdown of the inner blood–retina barrier and allowing fluid to accumulate in the interstitial space (Stewart 2012).

For decades, focal/grid photocoagulation was the primary treatment in DME (Blindbaek et al. 2019, 2020). Although it is still useful today, drugs inhibiting the effects of VEGF have taken its place in recent years as the main treatment in DME. This has drastically improved visual acuity in most patients (Blindbaek et al. 2019, 2020). However, a high number of intravitreal injections, ranging from 6 to 11 within the first year of treatment (Elman et al. 2010; Diabetic Retinopathy Clinical Research et al. 2015), are needed to sustain visual improvement (Elman et al. 2010). The frequent injections are a strain to the patients and expensive to the healthcare system (Ross et al. 2016; Grauslund & Blindbaek 2017), given the average need of 17 injections within 5 years (Elman et al. 2015).

Recently, our research group conducted the 12-month randomized controlled trial (RCT) 'Aflibercept and navigated versus conventional laser in diabetic macular oedema: a 12-month randomized clinical trial' (ADDENDUM), comparing the efficacy of intravitreal aflibercept and navigated focal/grid photocoagulation to intravitreal aflibercept and conventional focal/grid photocoagulation in DME patients. With a mean of just 4.4 intravitreal injections of aflibercept over 12 months, the patients gained 8.4 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in best corrected visual acuity (BCVA). While the study did not meet the primary endpoint of a better clinical outcome for those treated with navigated focal/grid photocoagulation, it did indicate that with proper timing of focal/grid photocoagulation in combination with aflibercept, the need for intravitreal therapy might be less than traditionally reported (Blindbaek et al. 2019, 2020).

The study was limited by the fact that a control group receiving standard-of-care intravitreal injections and focal/grid laser *pro re nata* (PRN) was not included. Therefore, the purpose of this study was to evaluate treatment efficacy in DME comparing the study population from ADDENDUM receiving intravitreal inhibition of vascular endothelial growth factor (VEGF) and postloading focal/grid photocoagulation with a matched, real-world population in our clinic receiving standard-of-care treatment. The aim was to assess the numbers of intravitreal anti-VEGF injections during the first 12 months of treatment as primary outcome, and differences in BCVA and central retinal thickness (CRT) from baseline to follow-up as secondary outcomes.

Materials and Methods

Based on a prespecified sample size calculation, we have previously performed the ADDENDUM study (Blindbaek et al. 2020). In ADDENDUM, the patients received three monthly intravitreal injections of aflibercept in the loading phase. At month 3, either navigated or conventional focal/grid photocoagulation was conducted. From month 4 through month 12, patients were examined monthly and additional intravitreal injections were given, if CRT had increased with more than 20% from lowest measurement, or if BCVA dropped more than five ETDRS letters compared to baseline (Blindbaek et al. 2019, 2020).

As we wanted to recruit a matching real-world population for this retrospective registry study, we had to identify the patients in our clinic at Odense University Hospital, Denmark, who fulfilled the same criteria of eligibility, but who did not participate in ADDENDUM. These criteria were as follows: clinically detected DME, age above 18 years, BCVA between 35 and 80 ETDRS letters and CRT $\geq$300 μm in the study eye. We excluded patients who were pregnant, had active proliferative DR or had received intraocular surgery or retinal photocoagulation within 4 months prior to inclusion (Blindbaek et al. 2019, 2020).

Between February and June 2020, a total of 111 patients who attended our clinic received written and oral information about our study and its purposes and agreed to sign a consent form granting the researchers access to retrospectively collect information in the electronic journals. Every journal was then systematically screened for information regarding date of referral to our clinic, type and duration of diabetes, body mass index (BMI), blood pressure, haemoglobin A1c, measurements of BCVA and CRT, dates of administration of intravitreal anti-VEGF therapy and photocoagulation or intraocular surgery. Baseline information was obtained from the control visit prior to the first intravitreal injection. There was no requirement for a loading phase in the real-world population. As it was retrospectively not possible to collect data from every patient exactly 12 months after their first visit, follow-up information regarding BCVA and CRT had to be obtained from whichever control visit that was closest to 12 months from the time of the first injection and the subsequent 10–15 months. However, to avoid bias of overestimating injection numbers in the real-world population, numbers of intravitreal injections were counted only up to the month of the 1-year mark.

Information was registered in a preapproved database (Oculus). Patients had to have received intravitreal therapy with VEGF inhibitors (aflibercept or ranibizumab) and had to have data from both BCVA and CRT from the same visit to be included in the real-world group.

After the exclusion of patients with missing data at baseline or follow-up, and patients who received surgery in the study eye during follow-up, a total of 46 eyes from 38 patients could be included in our study constituting the real-world population (Fig. 1).
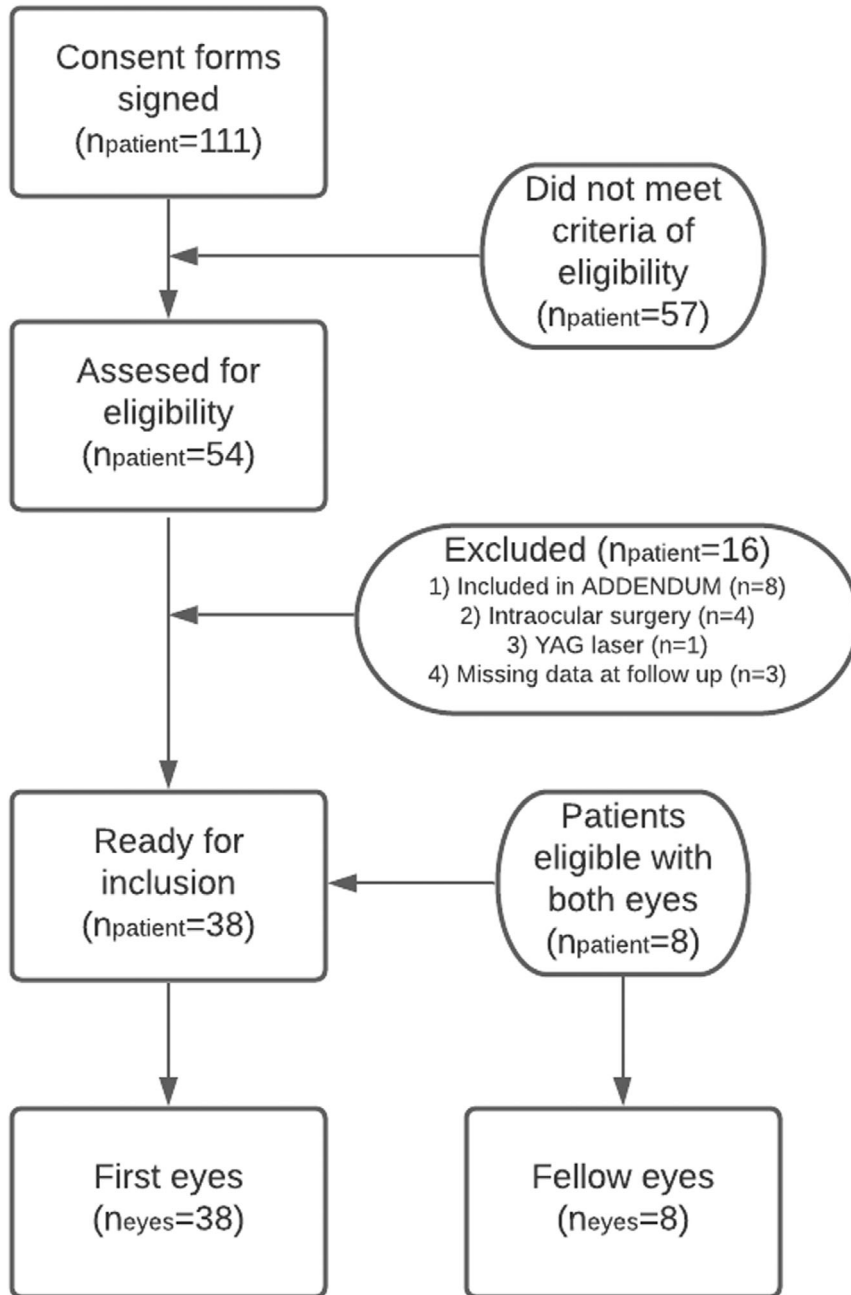
Fig. 1. Flowchart outlying the process of including patients in the real-life population.

Complications such as endophthalmitis, vitreous haemorrhage, cataract surgery or elevated intraocular pressure due to intravitreal injections were registered, if any of these happened during the follow-up period.

Statistical analysis

Statistical analyses were performed using STATA 15.0 (StataCorp LP, College Station, TX, USA). Continuous data are presented as mean (with 95% confidence interval [CI]) and categorical data as per cent (with numbers).

For calculations of statistical differences between continuous variables in Tables 1 and 2, we used a linear regression model with cluster-robust standard errors to account for the potential inclusion of more than one eye per patient. Study groups were used as explanatory variables, and clinical outcomes (i.e. BCVA and CRT) were used as dependent variables. In Table 2, adjustments were made for duration of diabetes and diastolic blood pressure to account for baseline differences between groups for these parameters. Fisher's exact test was used for

comparison of proportions. All calculations were made by eye (and not by person). p-values below 0.05 were considered statistically significant.

Results

We included data from 89 eyes of 70 patients (43 eyes of 32 patients in the study group and 46 eyes of 38 patients in the real-word group). Fewer eyes in the study group had received central photocoagulation prior to baseline than in the real-world group (14.0% (6 eyes) versus 37.0% (17 eyes), p = 0.02).

At baseline, there was no statistical significant differences between groups regarding age, sex, BMI, HbA$_1$c, systolic blood pressure and type of diabetes, but the study population had had diabetes for fewer years than in the real-world group (12.3 (95%CI 8.1–16.4) versus 23.2 (95%CI 15.0–31.4) years, p = 0.03) and had a higher diastolic blood pressure at baseline (81.6 (95%CI 77.1–86.2) versus 72.1 (95%CI 65.2–78.9) mmHg, p = 0.03; Table 1).

As per protocol, all eyes of the study group were treated with aflibercept, whereas eyes of the real-world group had either been treated with aflibercept (28 eyes) or ranibizumab (18 eyes). In the study group, every eye received photocoagulation during the follow-up period as dictated by the study design, compared to only five eyes in the real-world group (100.0% versus 10.9%, p < 0.01). None of the eyes in the study group received a dexamethasone implant during follow-up, as opposed to one eye in the real-world group (0.0% versus 2.2%, p = 1.00).

At month 12, patients in the study group had received fewer intravitreal aflibercept injections (4.4 (95%CI 3.9–4.8) versus 5.9 (95%CI 5.3–6.5), p < 0.01) and were more likely only to have received the three mandatory injections in the loading phase (39.5% versus 13.0%, p = 0.01) (Table 2). At month 12, the eyes in the study group had a higher BCVA than the eyes in the real-world group (79.6 (95%CI 76.1–83.1) versus 74.3 (95%CI 69.1–79.5) ETDRS letters, p = 0.03), but the changes from baseline to follow-up did not differ statistically (+8.4 (95% CI +6.8–9.9) versus +5.8 (95%CI +2.4–9.3) ETDRS letters, p = 0.19). No differences in CRT were observed

Table 1. Baseline characteristics for all eyes included in the study group and in the real-world population.

Variable	Total	Study group	Real-world	p
Patients, number	70	32	38	
Eyes, number	89	43	46	
Age, years	63.9 (60.2–67.5)	63.5 (58.9–68.0)	64.4 (58.1–70.8)	0.49
Sex, % male	65.2 (58)	67.4 (29)	63.0 (29)	0.82
Diabetes duration, years	16.7 (12.4–21.1)	12.3 (8.1–16.4)	23.2 (15.0–31.4)	0.03*
Type 2 diabetes	89.9 (80)	95.3 (41)	84.8 (39)	0.16
Haemoglobin A_1c, mmol/mol	60.8 (56.1–65.5)	61.4 (54.5–68.4)	59.9 (53.7–66.1)	0.49
Systolic blood pressure, mmHg	137.9 (133.4–142.5)	140.9 (135.1–146.7)	133.7 (126.7–140.7)	0.51
Diastolic blood pressure, mmHg	77.7 (73.6–81.8)	81.6 (77.1–86.2)	72.1 (65.2–78.9)	0.03*
Body mass index, kg/m^2	29.5 (27.8–31.3)	29.3 (26.8–31.7)	29.9 (27.2–32.6)	0.78
Previous photocoagulation, % of eyes	25.8 (23)	14.0 (6)	37.0 (17)	0.02*

All data presented per eye as continuous data given as means (with 95% confidence interval) or categorical data given as per cent (with numbers). Statistical differences between groups tested in a linear regression model with cluster-robust standard errors (for continuous variables) and Fisher's exact test (for categorical variables).
* indicate statistically significant values.

Table 2. Baseline (BL) and 12-month follow-up (M12) characteristics for all eyes included in the study group and in the real-world population.

Variable	Total	Study group	Real world	p
Patients, number	70	32	38	
Eyes, number	89	43	46	
Visual acuity BL, ETDRS letters	69.7 (67.0–72.4)	71.2 (68.3–74.2)	67.4 (62.4–72.4)	0.17
Visual acuity M12, ETDRS letters	77.4 (74.4–80.5)	79.6 (76.1–83.1)	74.3 (69.1–79.5)	0.03*
Visual acuity M12-BL, ETDRS letters	7.1 (5.1–9.0)	8.4 (6.8–9.9)	5.8 (2.4–9.3)	0.19
Improvement ≥5 ETDRS letters, %	73.0 (65)	81.4 (35)	65.2 (30)	0.10
Improvement ≥10 ETDRS letters, %	39.3 (35)	39.5 (17)	39.1 (18)	1.00
Improvement ≥15 ETDRS letters, %	22.5 (20)	16.3 (7)	28.3 (13)	0.21
Central retinal thickness BL, μm	398.8 (373.8–423.7)	388.4 (358.7–418.2)	413.7 (369.6–457.9)	0.34
Central retinal thickness M12, μm	291.0 (276.7–305.4)	290.5 (273.5–307.4)	291.9 (264.8–318.9)	0.31
Central retinal thickness M12-BL, μm	100.7 (78.4–122.9)	97.4 (71.1–123.7)	103.7 (68.3–139.1)	0.78
Number of injections from BL to M12, n	5.2 (4.7–5.6)	4.4 (3.9–4.8)	5.9 (5.3–6.5)	<0.01*
Total number of injections = 3, %	25.8 (23)	39.5 (17)	13.0 (6)	0.01*
Photocoagulation follow-up, %	53.9 (48)	100.0 (43)	10.9 (5)	<0.01*
Dexamethasone treatment, %	1.1 (1)	0.0 (0)	2.2 (1)	1.00

All data presented per eye as continuous data given as means (with 95% confidence interval) or categorical data given as per cent (with numbers). Statistical differences between groups tested in a linear regression model with cluster-robust standard errors and adjusted for duration of diabetes and diastolic blood pressure (for continuous variables) and Fisher's exact test (for categorical variables).
* indicate statistically significant values.

between the two groups at baseline (290.5 (95%CI 273.5–307.4) versus 291.9 (95%CI 264.8–318.9) μm, p = 0.31), and both groups had similar developments during follow-up (−97.4 (95%CI 71.1–123.7) versus −103.7 (95%CI 68.3–139.1) μm, p = 0.78). Duration of follow-up was exactly 12 months in the study group and 12.5 months in the real-world group (standard deviation 1.35 months, p < 0.01).

Discussion

With this exploratory longitudinal study, we demonstrated that despite the need for 25% fewer intravitreal aflibercept injections, the study population from ADDENDUM obtained a better postoperative BCVA as compared to a matched real-world group. Furthermore, ADDENDUM patients were 27% more likely to defer further treatment after the three injections of the loading phase and focal/grid photocoagulation. Despite the exploratory nature of the study, this is clinically interesting, as most attempts to combine retinal photocoagulation and intravitreal therapy have not been able to reduce the need for intravitreal injections.

In the RESTORE study, Mitchell et al. tested the combination of ranibizumab and photocoagulation against both photocoagulation monotherapy and ranibizumab monotherapy over the course of 12 months in a large RCT including 345 patients. In the combination group, patients gained a mean of 5.9 ETDRS letters with a mean of 6.8 intravitreal injections of ranibizumab administered during the 12 months, but combination therapy was not superior to ranibizumab monotherapy (Mitchell et al. 2011). In the TREX-DME study, Payne et al. tested monthly dosing of ranibizumab against a treat and extend regimen both with and without angiography-guided macular photocoagulation in 150 eyes. In the combination group, a mean of 10.1 intravitreal injections led to an improvement in BCVA of 9.5 ETDRS letters after 1 year, but the addition of photocoagulation did not improve injections numbers, BCVA or CRT (Payne et al. 2017). The DRCR.net Protocol I trial demonstrated a need

for nine intravitreal injections during the first year of treatment with no differences between treatment arms of monotherapy versus combination therapy (Elman et al. 2010). Likewise, seven injections were administered in the REVEAL study during the first year in the combination arm (Ishibashi et al. 2015).

In a 12-month prospective trial, Liegl et al. tested ranibizumab monotherapy against combined therapy of ranibizumab and navigated photocoagulation and reported similar improvements in BCVA between the two treatment groups (+8.4 versus +6.3 ETDRS letters, p = 0.26), but with a need for fewer injections in the combination group (3.9 versus 6.9, p < 0.01). As in ADDENDUM, a loading phase with three monthly injections was completed before the patients in the combination group additionally received navigated photocoagulation (Liegl et al. 2014). In ADDENDUM, a mean of 4.4 intravitreal aflibercept injections were needed to obtain similar improvements in BCVA. However, mean BCVA at baseline was considerably lower in the study by Liegl et al. compared to ADDENDUM (30.8 ± 12.6 ETDRS letters versus 71.3 ETDRS letters (68.6–74.0)), which could lead to a larger margin of BCVA improvement in the former study.

Promising results were also reported by Inagaki et al., who conducted a retrospective longitudinal study with 34 eyes from 31 patients on the combination of minimally invasive photocoagulation treatment and anti-VEGF therapy. They reported a gain of 5.9 ETDRS letters in BCVA during 12 months when administering a mean of just 3.6 intravitreal anti-VEGF injections (Inagaki et al. 2019). While these patients had equally good vision at baseline compared to the patients in ADDENDUM, the change in BCVA from baseline to follow-up did not quite match the +8.4 ETDRS letters reported in both ADDENDUM (Blindbaek et al. 2019, 2020) and by Liegl et al. (2014).

Regardless of some promising results, there has been a disunity in reports to whether the addition of photocoagulation to a treatment algorithm with anti-VEGF injections is an advantage or not. Comparison of outcomes between studies is complicated because of considerable differences in baseline BCVA. Also, different approaches to combination therapy have been used across studies. One being photocoagulation administered prior to or within the first few days after administering the first anti-VEGF injection as was done in one treatment arm in Protocol I as well as in the RESTORE and REVEAL studies (Elman et al. 2010; Mitchell et al. 2011; Ishibashi et al. 2015). Another approach, used in another arm in Protocol I, is deferred/rescue focal/grid photocoagulation, usually not permitted until week 24 and reserved for those who do not respond adequately to anti-VEGF monotherapy (Elman et al. 2010). In ADDENDUM, a loading dose of three monthly injections of aflibercept preceded focal/grid photocoagulation and visual outcome was equally good using either conventional or navigated photocoagulation (Blindbaek et al. 2019, 2020). Correspondingly, a loading dose of three monthly injections was used by Liegl et al. before administering photocoagulation, indicating that the timing of photocoagulation might be the key to achieve these promising results. We know that the benefits of photocoagulation in DME may be limited by macular fluid accumulation (Nguyen et al. 2010), and a larger effect of the photocoagulation may be seen upon a loading dose of intravitreal anti-VEGF therapy, when the oedema is reduced adequately.

A potential explanation to the better outcome in the study population compared to the real-world group in our study may be the fact that every eye in the study group received photocoagulation during follow-up as compared to only five eyes in the real-world group. The long-term benefits of retinal photocoagulation have been demonstrated in the Early Treatment Diabetic Retinopathy Study research group (1985), and our study indicates that timely treatment after intravitreal loading may reduce the need for further treatment.

Potential limitations to our study include the relatively low number of patients, the retrospective nature of the evaluation of the real-world cohort, and baseline imbalances of diabetes duration and previously administered retinal photocoagulation. Likewise, all clinical decisions in the real-world population were based on clinical estimates of the treating ophthalmologists, as there are no national guidelines to indicate exactly when treatment should be given. In the real-world group, 39% of eyes had been treated with ranibizumab instead of aflibercept, although we do not expect this to have any influence of results given the similar efficacy of the drugs, as previously demonstrated (Diabetic Retinopathy Clinical Research et al. 2015). Based on these limitations, the study might have had limited power to detect potential differences between groups, and p-values should be considered with caution.

In a direct comparison between a study population receiving predefined combination therapy of intravitreal aflibercept and focal/grid photocoagulation to a matched real-world population, we have shown that with 25% fewer injections, the patients in the study group obtained a better functional outcome. Furthermore, a larger proportion of the eyes in the study group had no need for extra injections after the loading phase. As frequent injections with anti-VEGF agents can be a burden to the patients and expensive to the healthcare system, the advantage of combining anti-VEGF therapy with laser therapy might be found in the potential to reduce the numbers of injections while obtaining an equally good visual outcome.

Studies with longer follow-up times are needed to investigate potential long-term cost–benefits of using fewer intravitreal anti-VEGF injections than in similar studies published so far. Future studies also need to address combination therapy with different timings of photocoagulation therapy versus anti-VEGF monotherapy in a randomized controlled setting during more than 12 months.

Ethical Approval

The study protocol was presented to the Regional Scientific Ethical Committee for Southern Denmark. It was decided that ethical approval was not required. Informed consent from the participants was acquired prior to the trial. The study was completed in accordance with the Tenets of the Declaration of Helsinki.

Acknowledgement

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