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ORIGINAL RESEARCH

One-Year Outcomes of Aflibercept in Treat-and-Extend Versus Pro Re Nata Regimens for Bevacizumab-Resistant Diabetic Macular Edema: A Real-World Study

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ABSTRACT

Introduction: The aim of this study was to compare the efficacy of the treat-and-extend (TAE) regimen versus the pro re nata (PRN) regimen in patients with bevacizumab-resistant diabetic macular edema (DME) treated with aflibercept, with or without adjunctive laser therapy.

Methods: Ninety-one eyes from 91 patients who were switched to aflibercept after three consecutive intravitreal bevacizumab injections for the treatment of DME were included in this retrospective real-world study. The patients were categorized into three groups: TAE ($n=30$), TAE + laser ($n=31$), and PRN ($n=30$). Changes in best-corrected visual acuity and central macular subfield thickness (CMST) at 12, 24, and 52 weeks were defined as the primary functional and anatomical outcomes.

Results: A total of 91 eyes from 91 patients (49.5% female) with a mean age of 63.9 ± 7.1 years were included in the analysis. At 52 weeks, the mean letter gains were 8.03, 8.90, and 10.23 in the TAE, TAE + laser, and PRN groups, respectively. Anatomical improvements, as measured by CMST reduction, were 55.33 µm, 33.35 µm, and 48.96 µm in the TAE, TAE + laser, and PRN groups, respectively. The average number of injections administered was 7.7, 8.1, and 8.1, respectively. The final extension interval for the TAE group was 8.7 weeks, compared to 9.5 weeks in the TAE + laser group.

Conclusions: The PRN group demonstrated the highest functional improvement while the TAE group showed the greatest anatomical improvement. Overall, both anatomical and functional outcomes in the TAE regimen were comparable to the PRN regimen in patients with bevacizumab-resistant diabetic macular edema.

Keywords: Aflibercept; Bevacizumab-resistant; Diabetic macular edema; Pro re nata regimen; Real-world study; Treat-and-extend regimen

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-024-01067-x.

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Key Summary Points

Why carry out this study?

In some countries, bevacizumab is used as the first treatment option for diabetic macular edema (DME), whether mandatory or not.

In bevacizumab-resistant DME cases frequently encountered by clinicians, a switch to aflibercept is often preferred, though the effectiveness of the chosen regimen remains a subject of inquiry: "Treat-and-Extend" (TAE) or "pro re nata" (PRN)?

What was learned from the study?

The 52-week results, though relatively early, suggest that the TAE regimen for aflibercept is non-inferior to the PRN regimen in this patient group.

Although both anatomical and functional outcomes in the TAE regimen were comparable to the PRN regimen, the PRN regimen showed a slight advantage in functional results, while the TAE regimen was a step ahead anatomically.

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of vision impairment due to diabetic retinopathy (DR) and represents the most common cause of permanent vision loss among working-age adults with diabetes [1, 2]. For many years, focal/grid laser photocoagulation was the standard treatment for DME, following its success in reducing severe vision loss in the Early Treatment Diabetic Retinopathy Study (ETDRS) [3]. However, the advent of intravitreal anti-vascular endothelial growth factor (VEGF) therapy has revolutionized DME management, spurring numerous clinical studies. Major trials have demonstrated superior anatomical and functional outcomes with bevacizumab (Avastin), ranibizumab (Lucentis), and aflibercept (Eylea), typically administered using specific treatment regimens [4–6]. Currently, clinicians commonly adopt either a pro re nata (PRN) regimen, where patients are monitored through regular visits and treated based on signs of disease activity, or a treat-and-extend (TAE) regimen, which allows for gradual extension of treatment intervals depending on disease stability. While the best visual outcomes are typically achieved with consistent monthly dosing, studies have shown that less frequent dosing can still effectively reduce retinal thickness and improve vision [7–10]. In the PRN regimen, the number of anti-VEGF injections is minimized, as treatment is only administered when signs of disease activity are observed. However, the requirement for regular monthly visits can be burdensome for both patients and clinicians. In contrast, the TAE regimen was developed to maintain the therapeutic benefits of anti-VEGF treatment while reducing the frequency of clinic visits. The TAE approach provides a personalized treatment schedule that progressively increases intervals between injections to determine the longest effective interval without disease recurrence. It typically begins with 3–5 monthly loading doses, after which macular edema is monitored using optical coherence tomography (OCT), and the intervals are extended by 2 weeks or 1 month. Once the longest effective interval is identified, fixed-interval injections are administered.

The TREX-DME and RETAIN studies demonstrated the effectiveness of the TAE regimen with ranibizumab in the treatment of diabetic macular edema (DME) [8, 9]. Sugimoto et al. further investigated the effectiveness of bevacizumab within a TAE regimen for DME, reporting significant visual improvement [11]. Additionally, the VIBIM study evaluated the use of aflibercept with the TAE regimen in DME management, concluding that the TAE regimen was non-inferior to a fixed-dose regimen [10]. Despite these findings, there are still a limited number of real-world studies assessing aflibercept in DME patients treated with the TAE regimen, particularly in comparison with the PRN regimen.

Hence, we aimed to investigate the early outcomes of patients with DME resistant to bevacizumab who were switched to aflibercept, comparing those treated with the TAE regimen, with or without laser, to those treated with the PRN regimen.

METHODS

Study Design and Patients

This retrospective, single-center, real-world study included 91 eyes from 91 patients who were switched to aflibercept after three consecutive intravitreal bevacizumab injections for the treatment of DME. Patients were selected by randomization through systematic and consecutive assignment of patients according to patient records. The primary objective of this study was to evaluate the differences between these two regimens, and to assess their respective advantages, if any, based on archived records. Changes in best-corrected visual acuity and central macular subfield thickness (CMST) at 12, 24, and 52 weeks were defined as the primary functional and anatomical outcomes.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional review board approval was obtained from the local Clinical Research Ethics Committee (IRB number:2023-KAEK-92). Informed consent was obtained from all patients.

Inclusion and Exclusion Criteria

Adult patients aged 18 years or older with type 1 or type 2 diabetes, presenting with DME involving the fovea and a CMST of ≥ 300 µm on OCT, were eligible for enrollment. Additional inclusion criteria required a best-corrected visual acuity (BCVA) between 24 and 72 letters on the ETDRS letter score. Only one eye was designated as the study eye, and if both eyes met the criteria, the eye with the worse visual acuity was selected.

The main exclusion criteria were: (1) a history of vitreoretinal surgery in the study eye, (2) the presence of retinal diseases other than DME, (3) prior intra-/periocular steroid use, (4) previous intravitreal anti-VEGF treatment (except for three consecutive intravitreal bevacizumab as mentioned), (5) prior laser photocoagulation in the study eye, and (6) corneal and/or lens opacities that could interfere with OCT imaging, (7) spherical error greater than 3.00 diopters, and (8) axial length greater than 25 mm and less than 21 mm.

Treatment and Assessment Schedule

At baseline, patient demographics, including age, sex, hemoglobin A1c levels, and diabetes duration, were recorded. Comprehensive ophthalmological examinations were conducted at each visit, including anterior and posterior segment slit-lamp biomicroscopy, BCVA in ETDRS letter score, and intraocular pressure (IOP) measurements via non-contact air tonometry. Additionally, color fundus photography and spectral-domain OCT (Cirrus HD-OCT 5000, Carl Zeiss Meditec AG, Jena, Germany) were performed at every visit. Fundus fluorescein angiography and color fundus imaging (TRC-50DX, Topcon Corporation, Tokyo, Japan) were used to evaluate fundus angiographic features and determine the need for laser treatment. CMST was measured using OCT and only patients with a signal strength of 7/10 or higher were included in the study. The foveal center was identified using an automated fovea localization algorithm on the OCT fundus image. The examination protocol comprised a 6 × 6-mm macular cube centered on the fovea, consisting of 128 horizontal B-scans, each containing 512 A-scans. Retinal thickness values for each of the nine areas corresponding to the ETDRS grid were automatically calculated using the Cirrus OCT software (Carl Zeiss Meditec AG, Jena, Germany). The Macular Thickness Analysis software of Cirrus OCT uses the internal limiting membrane (ILM) and the posterior aspect of the retinal pigment epithelium (RPE) as reference layers for central macular thickness measurements.

Due to insurance policy requirements, patients with DME were mandated to receive three initial bevacizumab injections as part of their primary treatment currently in this land. Following the bevacizumab loading phase, disease activity was assessed, and patients who demonstrated persistent activity and were

resistant to intravitreal bevacizumab were switched to aflibercept therapy. In this study, resistant DME was defined as central macular subfield thickness (CMST) ≥ 300 µm with persistent or increasing subretinal or intraretinal fluid, or a loss of ≥ 5 letters compared to baseline, despite receiving three consecutive bevacizumab injections. Patients switched to aflibercept received three consecutive monthly injections as a loading dose. Following the aflibercept loading phase, patients were divided into three groups: aflibercept without laser (TAE, $n=30$), aflibercept with laser (TAE + laser, $n=31$), and PRN ($n=30$). All intravitreal injections were performed with local anesthetic (tetracaine) under sterile room conditions.

TAE Protocol

Patients in the TAE protocol group received three consecutive 2-mg aflibercept injections every 4 weeks during the "loading phase" after which they transitioned to TAE regimen. The interval between injections was adjusted in 2-week increments based on disease activity, as assessed by OCT and BCVA. Following the loading phase, patients in the TAE group could extend their follow-up and treatment intervals if OCT showed no signs of disease activity and BCVA was either stable or improved compared to the previous visit. Starting from an initial 2-week interval, the follow-up interval was extended by 2 weeks each time, with a maximum interval of 16 weeks. An injection was administered at every visit. New disease activity was defined as a loss of ≥ 5 letters on the ETDRS chart or ≥ 10% increase in CMST. If new disease activity was detected on OCT, the treatment interval was reduced by 2 weeks. In the TAE regimen, if CMST remained stable for two consecutive visits and visual stabilization continued, the interval between treatments was gradually extended to a maximum of 16 weeks. If no worsening of DME occurred during this period, treatment was deferred, and the follow-up interval was shortened to 8 weeks.

TAE + Laser Protocol

In the TAE + laser group, laser treatment was applied according to the modified ETDRS guidelines [12]. Focal/grid laser treatment was allowed as a rescue therapy at the discretion of the treating physician if CSMT increased by up to 10% from baseline or if BCVA decreased by more than ten letters due to DME at 24 weeks or later, reflecting a real-world late-stage laser treatment approach. There is no laser session limitation. Laser sessions were performed using a 577-nm laser photocoagulation device (Supra Scan®; Quantel Medical, Cournon-d'Auvergne, France).

PRN Protocol

Patients in the PRN protocol group received three consecutive intravitreal injections of 2-mg aflibercept every 4 weeks during the "loading phase". After this phase, the PRN protocol was applied, with monthly injections continuing until no disease activity was observed on OCT and BCVA improved or stabilized compared to the previous visit. Following stabilization, patients entered a regular follow-up schedule, typically every 1 to 3 months, as determined by the treating physician in consultation with the patient. No additional injections were administered unless a recurrence of disease activity was detected on OCT during the follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS software, version 22.0 (IBM SPSS, Chicago, IL, USA). The Shapiro–Wilk test was employed to assess the normality of data distribution. Descriptive statistics, including percentages, means ± standard deviation, or medians with interquartile range (IQR), were used to summarize baseline characteristics based on the normality of the data. For nominal variables, the chi-square test was applied. When comparing the three groups, a one-way ANOVA was used for normally distributed data, while the Wilcoxon signed-rank test and Kruskal–Wallis test were used for non-normally distributed data. Using G*Power software (version 3.1.9.7), with a medium effect size of $f=0.34$, an alpha level of $p=0.05$, a power of $1-\beta=0.80$, and three groups,

the power analysis for ANOVA indicated a required total sample size of $n=87$ participants. Therefore, the three groups were arranged to include approximately 30 patients each. All evaluations were conducted with a 95% confidence interval, and p values less than 0.05 were considered statistically significant.

RESULTS

Patient Demographics and Baseline Characteristics

The study included 45 females (49.5%) and 46 males (50.5%) with a mean age of 63.9 ± 7.1 years. A total of 91 eyes from 91 Caucasian patients were analyzed. The average duration of diabetes was 15.9 ± 5.9 years, and the mean HbA1c (%) was 8.79 ± 1.69. Baseline characteristics were comparable across the groups ($p>0.05$). Detailed demographic, diabetic, and ocular characteristics at baseline are provided in Table 1. In TAE aflibercept + laser group, a single session of focal/grid laser treatment was sufficient for 24 patients, while two sessions were required for five patients, and three sessions were administered to two patients. There are no cases in this study population that are resistant to aflibercept.

Functional and Anatomical Outcomes

Best-Corrected Visual Acuity

At week 52, the mean letter gains were 8.03 in the TAE group, 8.90 in the TAE + laser group, and 10.23 in the PRN group. There was a statistically significant increase in vision in all groups compared to baseline (Table 2) ($p<0.05$ for all). However, there were no statistically significant differences in letter gains between the groups at the 12th-, 24th-, or 52nd-week visits (Table 3) ($p>0.05$ for all). Gains of ≥ 15 letters were achieved by seven, 11, and nine patients in the TAE, TAE + laser, and PRN groups, respectively.

Central Macular Thickness

CMST trended to decrease in all groups across visits (Fig. 1). When evaluating anatomical gain in terms of CMST reduction, the mean changes were 55.33 µm, 33.35 µm, and 48.96 µm in the TAE, TAE + laser, and PRN groups, respectively. A more significant anatomical gain was observed in the TAE group at the 24th week compared to the previous visit ($p=0.034$). No significant differences were found at other time points.

In the subgroup analysis shared in the supplementary file, which included only patients with type 2 DM ($n=80$), a statistically significant difference was observed between the three protocols in terms of CMST reduction at 24 and 52 weeks (Kruskal–Wallis test, $p=0.044$ and $p=0.029$, respectively) (Supplementary Tables 1–4). In the post hoc analysis, no significant differences were found between the PRN and TAE + laser groups, while a statistically significant difference was identified between the TAE and TAE + laser groups at both 24 and 52 weeks (Bonferroni, $p=0.047$ and $p=0.027$, respectively). However, there were no differences in BCVA change, number of injections, or last extension week. Additionally, in the subgroup analysis of only phakic patients, a statistically significant difference was found between the three groups regarding CMST reduction at 52 weeks (Kruskal–Wallis test, $p=0.043$) (Supplementary Tables 5–8). Post hoc analysis revealed a statistically significant difference between the TAE and TAE + laser groups (Bonferroni, $p=0.044$).

Complications

No major complications were observed in any of the patients, except for mild subconjunctival hemorrhage in 12 patients and severe subconjunctival hemorrhage in two patients.

DISCUSSION

This study provides real-world data comparing the TAE regimen with the PRN regimen following a switch to aflibercept therapy in patients

Table 1 Baseline demographic, diabetes, and ocular characteristics of the study population

	TAE aflibercept 2 mg (*n* = 30)	TAE aflibercept 2 mg + laser (*n* = 31)	PRN aflibercept 2 mg (*n* = 30)	*p* value
Age, years	65.7 ± 7.1	62.3 ± 5.6	63.5 ± 8.2	0.172[a]
Gender, *n* (%)				0.366[b]
Female	13 (43.3)	14 (45.2)	18 (60)	
Male	17 (56.7)	17 (54.8)	12 (40)	
HbA1c, %	8.6 ± 1.4	8.2 ± 1.5 (8.5, 7–9)	9.4 ± 1.8 (9.2, 8–10)	0.064[c]
Diabetes, *n* (%)				0.911[b]
Type I	3 (10)	4 (12.9)	4 (13.3)	
Type II	27 (90)	27 (87.1)	26 (86.7)	
DME, *n* (%)				0.843[b]
Focal	9 (30)	7 (22.6)	8 (26.7)	
Diffuse	21 (70)	24 (77.4)	22 (73.3)	
Diabetes duration, years	15.4 ± 6.4 (15, 10–20)	16.9 ± 5.7 (20, 15–20)	15.4 ± 5.4	0.198[c]
Lens status				0.242[b]
Phakic, *n* (%)	22 (73.3)	27 (87.1)	21 (70)	
Pseudophakic, *n* (%))	8 (26.7)	4 (12.9)	9 (30)	
CMST, μm	359.3 ± 43.1 (349.5, 326–391)	343.8 ± 30.1 (337, 323–355)	368.1 ± 48.7 (349.5, 337–393)	0.078[c]
BCVA, letters	59.8.1 ± 19 (65, 45–75)	62.5 ± 17.4 (65, 50–78)	58.2 ± 19.3 (60, 42–75)	0.706[c]
IOP, mmHG	16.1 ± 3.6	17.1 ± 2.6 (16, 15–18)	18.3 ± 2.7	0.063[c]

SD standard deviation, *BCVA* best-corrected visual acuity, *CMST* central macular subfield thickness, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IOP* intraocular pressure, *DM* diabetes mellitus, *DME* diabetic macular edema, *HT* hypertension. Mean ± standard deviation results are given in the table (additionally, median, 25th, and 75th percentiles are indicated in parenthesis for nonparametric test results). $p < 0.05$ was considered statistically significant in 95% confidence interval

[a]One-way ANOVA test

[b]Chi-square test

[c]Independent-samples Kruskal–Wallis test

with DME resistant to bevacizumab treatment. According to early results at 52 weeks, the PRN group showed the highest letter gain, while the TAE group demonstrated the greatest anatomical gain, as measured by CMST reduction. A gain of ≥ 15 letters was achieved by 27 of the

Table 2 Changes in best-corrected visual acuity and central macular subfield thickness within groups separately compared to baseline during the study and comparison of groups

BCVA, letters	TAE aflibercept ($n = 30$)	95% CI lower/upper values	Comparison from baseline p value	TAE aflibercept + laser ($n = 31$)	95% CI lower/upper values	Comparison from baseline p value	PRN aflibercept ($n = 30$)	95% CI lower/upper values	Comparison from baseline p value	Comparison of groups p value
Baseline	59.8.1 ± 19 (65, 45–75)	53.3/66.3	–	62.5 ± 17.4 (65, 50–78)	56/68.4	–	58.2 ± 19.3 (60, 42–75)	51.6/64.8	–	0.706[b]
12th week	64.7 ± 17.9 (71.5, 50–80)	58.4/70.8	0.009[a]	69.7 ± 16.7 (75, 59–83)	63.5/75.1	< 0.001[a]	65.3 ± 16.2 (70, 57–78)	59.7/71.1	0.009[a]	0.261[b]
24th week	66.2 ± 17.2 (72, 61–79)	59.9/72.1	0.007[a]	70.5 ± 13.7 (77, 63–80)	65.2/74.9	< 0.001[a]	68.6 ± 12.9 (72.5, 60–80)	64/72.9	< 0.001[a]	0.537[b]
52nd week	67.8 ± 14.2 (71.5, 66–75)	62.7/72.3	0.004[a]	71.4 ± 13.9 (77, 65–80)	66.5/75.7	< 0.001[a]	68.5 ± 16.7 (74.5, 60–81)	61.9/74.5	< 0.001[a]	0.344[b]
CMST, μm										
Baseline	359.3 ± 43.1 (349.5, 326–391)	345.3/374.9	–	343.8 ± 30.1 (337, 323–355)	334.8/355.1	–	368.1 ± 48.7 (349.5, 337–393)	352.6/386.1	–	0.078[b]
12th week	334.8 ± 35.5 (324.5, 307–354)	322.5/348.7	< 0.001[a]	332 ± 28.7 (320, 315–346)	323.3/342.6	< 0.001[a]	353.5 ± 36.5 (349, 321–376)	341.2/367.2	0.011[a]	0.01[b]
24th week	318.4 ± 48.4	301.5/334.6	< 0.001[a]	321.9 ± 28.9 (318, 304–331)	313.2/333.1	< 0.001[a]	342.3 ± 39.9	328.5/356.9	0.002[a]	0.032[b]
52nd week	304 ± 38.1	290.9/318.6	< 0.001[a]	310.5 ± 30.5 (307, 294–329)	299.8/321.6	< 0.001[a]	319.2 ± 41.4	305/334.7	< 0.001[a]	0.297[b]

SD standard deviation, *BCVA* best-corrected visual acuity, *CMST* central macular subfield thickness, *PRN* pro re nata, *TAE* treat-and-extend, *CI* confidence interval. Mean ± standard deviation results are indicated in the table (additionally, median, 25th, and 75th percentiles are given in parenthesis for nonparametric test results). $p < 0.05$ was considered statistically significant in 95% confidence interval

[a]Wilcoxon signed-rank test

[b]Independent-samples Kruskal–Wallis test

Table 3 Differences in best-corrected visual acuity and central macular subfield thickness values compared to baseline and course of treatment

	TAE aflibercept ($n = 30$)		TAE aflibercept + laser ($n = 31$)		PRN aflibercept ($n = 30$)		Comparison of groups
BCVA changes, letters		95% CI lower/upper values		95% CI lower/upper values		95% CI lower/upper values	p value
12th week	4.93 ± 11.4 (2, 0–9)	0.7/8.8	7.19 ± 7.3 (5, 0–11)	4.8/9.7	7.03 ± 14.1 (6, – 0.5–11.25)	2.5/11.9	0.599[a]
24th week	6.40 ± 11.5 (2.5, -0.5–11.75)	2.6/10.7	8.00 ± 9.3 (6, 2–15)	4.9/11.1	10.3 ± 13.9 (7.5, 2.75–15.5)	5.9/15.4	0.284[a]
52nd week	8.03 ± 13.5 (5, 0–12)	3.4/12.9	8.90 ± 10.3 (9, 0–15)	5.4/12.2	10.23 ± 18.3 (9, 0.75–20)	3.2/16.4	0.472[a]
Decrease in CMST, μm							
12th week	24.56 ± 22.3 (21, 10–30)	17.3/32.7	11.80 ± 18.3 (11, 4–20)	5.6/18.6	14.66 ± 32.7 (12, – 7.25–27)	3.8/25.5	0.058[a]
24th week	40.93 ± 34.4 (31.5, 19.75–55.25)	28.8/54.2	21.90 ± 25.4 (16, 10–23)	13/31.4	25.83 ± 40.5 (27.5, 7.25–51.25)	10.6/37.9	0.034[a]
52nd week	55.33 ± 40.6 (39.5, 30–78.75)	42.1/70.9	33.35 ± 27.5 (28, 18–43)	23.8/43.4	48.96 ± 36.7 (39.5, 18.25–70.5)	35.6/62.3	0.051[a]
Number of injections	7.7 ± 1.6 (8, 8–9)	7.1/8.2	8.1 ± 2.1 (8.5, 7–9)	7.3/8.8	8.1 ± 1.6 (8, 7–9)	7.5/8.6	0.565[a]
Last extension week	8.7 ± 1.6 (8, 8–8.5)	8.2/9.4	9.5 ± 1.8 (8, 8–12)	8.8/10.1	–	–	0.062[b]

SD standard deviation, *BCVA* best-corrected visual acuity, *CMST* central macular subfield thickness, *ETDRS* Early Treatment Diabetic Retinopathy Study, *PRN* pro re nata, *TAE* treat-and-extend, *CI* confidence interval. Mean ± standard deviation results are given in the table (additionally, median, 25th and 75th percentiles are given in parenthesis for nonparametric test results). $p < 0.05$ was considered statistically significant in 95% confidence interval (comparisons of groups)

[a]Independent-samples Kruskal–Wallis test

[b]Mann–Whitney *U* test

91 patients (29.6%). At the 52-week mark, the average final extension intervals in the TAE groups were 8.7 and 9.5 weeks. The findings from this study indicate that the TAE regimen is not inferior to the PRN regimen in managing bevacizumab-resistant cases, with both visual and anatomical gains maintained for over 12 months.

In both the VISTA and VIVID studies, the visual and anatomical superiority of aflibercept treatment with a fixed-dose regimen over laser control at 52 weeks was maintained through

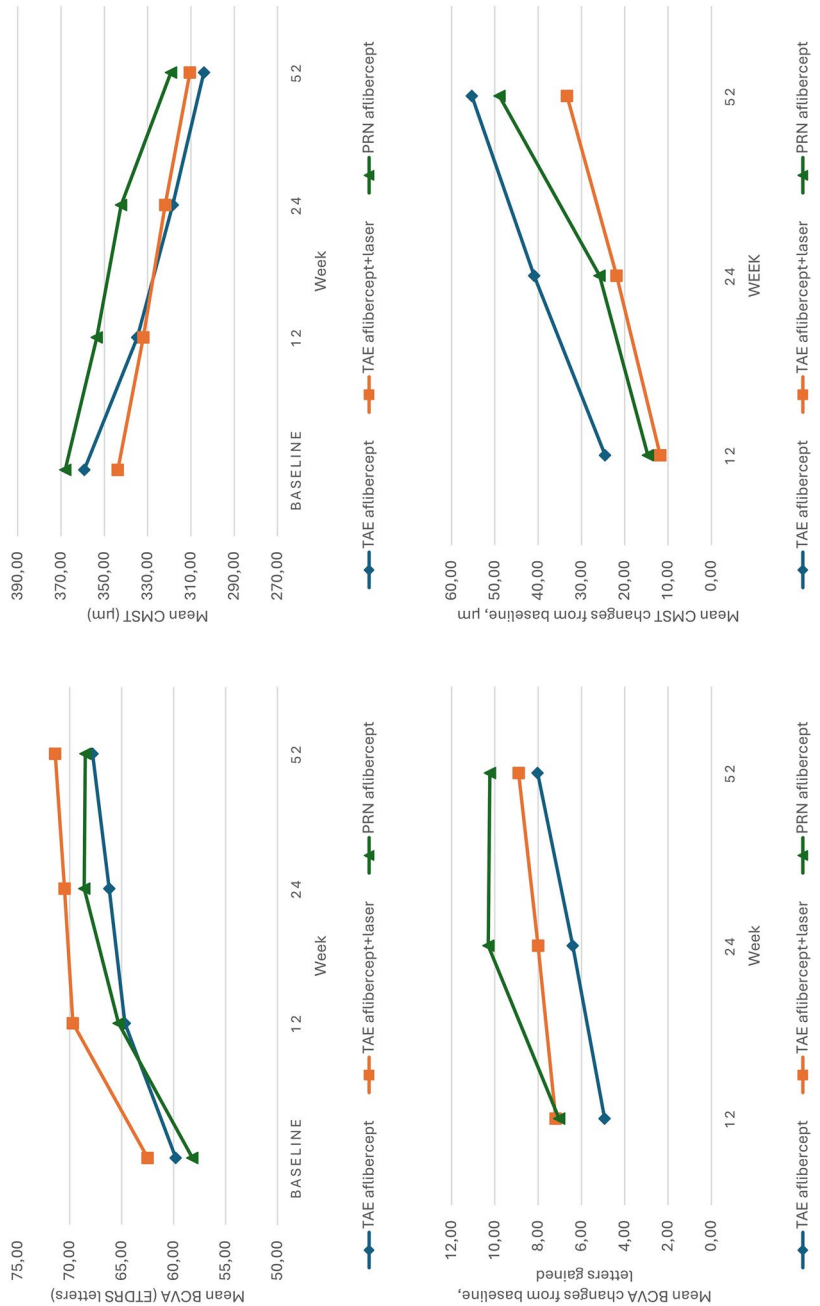

Fig. 1 Changes in best-corrected visual acuity (ETDRS letters) and central macular subfield thickness (µm) compared to baseline at the 12th week, 24th week, and 52nd week. *BCVA* best-corrected visual acuity, *CMST* central macular subfield thickness, *ETDRS* Early Treatment Diabetic Retinopathy Study, *PRN* pro re nata, *TAE* treat-and-extend

week 100, with similar efficacy observed in both the 2q4 and 2q8 groups [13]. In the VISTA study, mean BCVA gains from baseline to week 52 were 12.5 letters in the 2q4 group and 10.7 letters in the 2q8 group, while in the VIVID study, the gains were 10.5 and 10.7 letters, respectively. The DA-VINCI study reported mean BCVA improvements at week 52 of 13.1, 9.7, and 12.0 letters in the 2q4, 2q8, and 2PRN aflibercept treatment groups, respectively [14]. Similarly, the RETAIN study demonstrated that letter gains with the TAE regimen were not inferior to the PRN regimen, based on mean BCVA change through month 12 [9]. In the TREX-DME study, mean BCVA increased by 9.6, 9.5, and 8.6 letters at 1 year in the TAE, TAE + laser, and fixed-dose cohorts, respectively [15]. Additionally, the VIBIM study, which utilized aflibercept, reported a mean letter gain of 9.1 letters at 12 months with the TAE regimen [10]. In the current study, letter gains were 8.03, 8.9, and 10.2 in the TAE, TAE + laser, and PRN groups, respectively. Although the PRN group showed slightly higher gains, there were no statistically significant differences between the groups.

In the VISTA study, the proportion of eyes gaining ≥ 15 letters at week 52 was 41.6% in the 2q4 group and 31.1% in the 2q8 group, while in the VIVID study, the rates were 32.4% and 33.3%, respectively [13]. The DA-VINCI study reported rates of 45.5%, 23.8%, and 42.2% in the 2q4, 2q8, and 2PRN groups, respectively [14]. In the VIBIM study, this proportion was 28.3% [10]. In the present study, 29.6% (27/91) of patients achieved a gain of ≥ 15 letters at the end of week 52. The BCVA letter gains and the proportion of patients gaining ≥ 15 letters at week 52 in the current study were comparable to those reported in the aforementioned studies, which investigated both fixed-dose and TAE regimens.

Mean reductions in central retinal thickness were 185.9 µm and 183.1 µm in the VISTA study, and 195.0 µm and 192.4 µm in the VIVID study for the 2q4 and 2q8 groups, respectively [13]. At the end of 52 weeks, anatomical gains of 110.2 µm in RETAIN, 171.7 µm in VIBIM, and 146 µm in TREX-DME were reported for the TAE regimens [8–10]. In the current study, mean CMST changes at 52 weeks resulted in anatomical gains of 55.3 µm, 33.3 µm, and 48.9 µm in the TAE, TAE + laser, and PRN groups, respectively. Although our results are consistent with other studies, the partial quantitative discrepancy between our findings and those of other studies may be attributed to differences in measurement methods and devices, specifically the use of CMST and SD-OCT (Cirrus HD-OCT 5000, Carl Zeiss Meditec AG, Jena, Germany). Additionally, the patients in this study were switched to aflibercept due to resistance to bevacizumab, which may have contributed to the reduced anatomical gains observed. Smaller anatomical improvements might be expected in treatment-resistant cases. Moreover, the baseline CMST values in our study were lower than those in the other studies, which could also explain the quantitatively smaller gains. Overall, similar to the aforementioned studies, anatomical gains were achieved in all three groups compared to baseline, and the non-inferiority of the TAE regimen compared to the PRN regimen was confirmed.

In the VISTA and VIVID studies, the mean number of injections over 52 weeks in the 2q8 groups treated with aflibercept every 2 months following five loading doses was 8.4 and 8.7, respectively [13]. In the TREX-DME study, the mean number of ranibizumab injections was 10.7 in the TAE group, 10.1 in the TAE + laser group, and 13.1 in the fixed-dose group [8]. In the present study, the mean number of injections at 52 weeks was 7.7 in the TAE group, and 8.1 in both the TAE + laser and PRN groups. There was no statistically significant difference in the number of injections between the groups. The mean number of injections at 52 weeks is comparable to previous pivotal studies. One of the key questions remains whether the application of laser impacts the TAE regimen by reducing the number of injections or extending the last extension interval, but the results of this study show no significant difference (number of injections: 7.7 ± 1.6 vs. 8.1 ± 2.1 and last extension week: 8.7 ± 1.6 vs. 9.5 ± 1.8). On the other hand, in our subgroup analysis for only patients with type 2 DM, the difference in CMST reduction between the TAE and TAE + laser groups at 24 and 52 weeks may be attributed to the inflammatory response associated with

laser treatment. Additionally, the difference in CMST reduction between the TAE and TAE + laser groups in only phakic patients at 52 weeks could be related to the greater impact of phakic lenses on oxidative and inflammatory stress in the laser group. Of course, further studies are needed to explore these findings.

In the TREX-DME study, the final extension intervals were 8.1 weeks in the TAE group and 9.2 weeks in the TAE + laser group [8]. Similarly, the VIBIM study reported an average last extension interval of 10.7 weeks [10]. In the present study, at the end of 52 weeks, the mean final extension interval was 8.7 weeks in the TAE group and 9.5 weeks in the TAE + laser group. Most studies recommend an initial loading dose of five aflibercept injections for the treatment of DME, and in several studies evaluating aflibercept treatment and the TAE regimen, the switch to the TAE protocol occurred after five loading doses [10, 13, 16, 17]. In our study, after administering three loading doses of bevacizumab, we followed up with three loading doses of aflibercept, similar to the protocol used in the DAVINCI study [14]. These results represent early outcomes at 52 weeks, and it is anticipated that the treatment intervals will further increase, resulting in fewer injections.

This study had several limitations. The study's primary limitations include the small number of patients in each group, its retrospective design, and the fact that it evaluated patients who were switched from bevacizumab treatment rather than assessing the effectiveness of a single anti-VEGF agent. In addition, while these early results at 52 weeks offer valuable insights, the absence of long-term data, such as results at 104 weeks, can be considered a limitation. Moreover, functional assessment in this study was limited to visual acuity measurement with ETDRS letters; further studies incorporating microperimetric and electrophysiological functional tests are warranted. Furthermore, the fact that patients who received intravitreal corticosteroid rescue were not included in this study may be considered a limitation, as it affects the study's ability to fully reflect real-life scenarios. Also, the inclusion of a relatively small number of patients with type 1 DM (n=11) alongside patients with type 2 DM may have introduced bias, and this can also be considered a limitation of the study. In addition, despite being a real-life study, the absence of aflibercept-resistant cases in this study population may be considered another limitation. However, to the best of our knowledge, this study provides real-world insights into the use of aflibercept with a TAE regimen in patients with bevacizumab-resistant DME, especially where bevacizumab is started as the first treatment option, whether mandatory or not.

CONCLUSIONS

In summary, based on the 52-week results of this real-world study, no statistically significant differences were observed between the groups. However, the PRN group achieved the highest letter gain, while the TAE group showed the greatest anatomical improvement. Following a switch to aflibercept in patients with bevacizumab-resistant DME, both anatomical and functional outcomes of the TAE regimen were comparable to those of the PRN regimen. Further studies are needed to assess the long-term real-world efficacy and safety of aflibercept with the TAE regimen in patients with bevacizumab-resistant DME.

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Declarations

Conflict of Interest. All named authors confirm that they have no conflicts of interest to declare. Mehmet Cem Sabaner is an Advisory Editorial Board member of Ophthalmology and Therapy. He was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional review board approval was obtained from the local Clinical Research Ethics Committee (IRB number:2023-KAEK-92). Informed consent was obtained from all patients.

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