One-year outcomes of the treat-and-extend regimen using aflibercept for the treatment of diabetic macular edema

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ABSTRACT

Background: Optimal regimen using intravitreal aflibercept injections for diabetic macular edema (DME) in clinical practice remains to be elucidated. The purpose of this study is to evaluate a treat-and-extend (TAE) approach using intravitreal aflibercept in participants with center-involved DME.

Methods: A 52-week open-label, prospective, multicenter, interventional study was conducted between August 2015 and November 2017 in Taiwan. Adults with diabetes mellitus and center-involved DME who have best-corrected visual acuity (BCVA) of 73 to 24 Early Treatment Diabetic Retinopathy Study letters and central retinal thickness (CRT) >300 μm were included. Participants received five monthly loading doses of 2 mg intravitreal aflibercept, followed by a TAE regimen with a four-week increment/decrement interval over 48 weeks; the maximum interval was 12 weeks. Main outcomes included changes in BCVA and CRT from baseline to week 52, additional anatomical outcomes, and treatment burden parameters.

Results: Forty-five participants with mean (SD) age of 63.7 (8.3) years were analyzed. At baseline, mean (SD) BCVA and CRT were 58.3 (11.9) letters and 434.4 (116.8) μm, respectively. Changes from baseline in BCVA and CRT were +8.3 (9.3) letters and −138.2 (150.0) μm (both $p < 0.001$) at week 52, respectively. In addition, 22% (10/45) of patients gained ≥15 letters, 14% (6/44) of participants achieved ≥2-level improvement in diabetic retinopathy severity, and 51% (23/45) demonstrated dry retina at week 52 compared with 13% (6/45) at baseline. In total, 87% (39/45) of patients reached disease stability, entering TAE at week 20. Subsequently, 89% (40/45) of patients reached maximum interval at week 52. Mean (SD) number of injections was 7.7 (1.5) over a period of 52 weeks.

Conclusion: This straightforward and practical TAE regimen using intravitreal aflibercept injections resulted in favorable clinical outcomes with minimal treatment burden for DME at week 52.

Keywords: Adult; Humans; Prospective studies; Retina; Visual acquity

1. INTRODUCTION

Diabetic retinopathy (DR) is a major microvascular complication in patients with diabetes mellitus (DM). The prevalence of DR was estimated at 34.6% globally (approximately 93 million worldwide) with higher prevalence in the west (28.5%–40.3% in the United States) than in the east (12.1%–23.0% in most Asian countries) for type 2 DM (T2DM).[1–4] Diabetic macular edema (DME) represents one of the vision-threatening manifestations of DR and is the main cause of vision loss in T2DM. Among population-based studies, the prevalence of DME ranged up to 7.9% and 12.8% in T1DM and T2DM, respectively.[2] With the rising prevalence of DM, the burden of DME has gained considerable attention worldwide.[5]

Anti–vascular endothelial growth factor (VEGF) agents have evolved into one of the essential therapeutic approaches for DME. Several clinical trials using intravitreal agents, such as aflibercept, bevacizumab, and ranibizumab, have reported superior visual outcome compared with using laser photocoagulation.[6–11] Intravitreal anti-VEGF injections can be given as fixed dosing, pro re nata (PRN; as needed), or treat-and-extend (TAE) regimens. The majority of randomized controlled trials using these agents involved a fixed dosing regimen or protocol-specified PRN treatment with monthly monitoring.[12,13] In real-world practice, however, patient compliance/adherence and financial concern are potential issues affecting monthly visits and injections in long-term management.[14–17]

Treatment burden can be reduced when less frequent injections and/or clinic visits yield equivalent efficacy. The RETAIN study supported the feasibility of a TAE regimen using ranibizumab

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 246-251.

Received July 26, 2021; accepted September 30, 2021.

doi: 10.1097/JCMA.0000000000000680.

for DME.[18] Although the TAE regimen did not result in fewer injections, it reduced the number of clinic visits by 46%. The TREX-DME trial compared ranibizumab with monthly, TAE, and TAE + laser regimens for center-involved DME. At 1 year, both TAE with and without laser significantly reduced the number of injections while maintaining similar efficacy compared with monthly injections.[19] Two phase 3 trials of aflibercept, VISTA and VIVID, demonstrated similar outcomes in groups treated with 2 mg intravitreal aflibercept every 4 weeks (q4w) and every 8 weeks (q8w) after a loading phase of five monthly injections. This finding indicates the feasibility of an extended regimen with aflibercept.[6] Currently, the most suitable regimen for aflibercept following loading doses remains unclear. This study was conducted to investigate the clinical outcome and safety of a TAE regimen using intravitreal aflibercept in patients with DME in Taiwan.

2. METHODS

2.1. Study design

This 52-week phase 3b, multicenter, single-arm, open-label, prospective, interventional trial of participants with center-involved DME took place in five sites in Taiwan. It was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of each participating site. Written informed consent was obtained before enrollment.

2.2. Participants and treatments

Participants were adults aged ≥20 years with DM and center-involved DME (defined as the area of the center subfield of optical coherence tomography [OCT]). The spectral domain OCT machines used in the five centers were either Avanti RTVue XR (AngioVue Software; Optovue, Fremont, CA, USA) or Spectralis OCT (software version 5.6; Heidelberg Engineering, Dossenheim, Germany). The thickness measured by different OCT machines was converted to equivalent Zeiss stratus (Stratus = −43.55 + 0.98 × RTVue; Stratus = −72.76 + 1.03 × Spectralis).[20] Eligibility criteria included best-corrected visual acuity (BCVA) of 73 to 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/40 to 20/320 Snellen equivalent) and central retinal thickness (CRT) of >300 μm. Participants whose study eye received laser photocoagulation or anti-VEGF medications within 90 days or intra/periocular corticosteroids within 120 days before screening were excluded. One eye per participant was enrolled in the study. If both eyes of a participant met eligibility criteria, the eye with worse visual acuity (VA) was selected. The eligibility criteria are detailed in Supplementary Table 1 http://links.lww.com/JCMA/A126.

After enrollment, participants received five monthly (weeks 0, 4, 8, 12, and 16) loading doses of 2 mg intravitreal aflibercept injection, followed by TAE with a 4-week increment/decrement interval based on disease stability. The retreatment criteria were as follows: the next scheduled injection interval was either (1) extended by 4 weeks if there was VA loss of <5 letters since the previous visit or CRT <300 μm or (2) shortened by 4 weeks provided conditions of VA loss of ≥5 letters and CRT ≥300 μm were both met. The minimum and maximum intervals during the study were 4 and 12 weeks, respectively. Starting at week 24, if participants had VA loss of ≥15 letters since the best previous measurement and their actual BCVA was worse than baseline, additional treatments (eg, focal laser) other than prohibited medications (ie, other local or systemic medications intended for treating DME) could be prescribed at the investigator's discretion. Any treatment of the fellow eye followed the rules of routine medical care and was not part of this study; however, safety was monitored.

2.3. Assessment and outcome measurement

The primary end point was mean change in BCVA as assessed by ETDRS letter score from baseline to week 52. Secondary end points included (1) mean change in CRT from baseline as assessed by OCT at week 52, (2) proportion of participants who gained ≥15 letters at week 52, (3) proportion of participants with ≥2-level improvement in DR severity[21] as assessed by 7-field color fundus photography at week 52 (see Supplementary Table 2 http://links.lww.com/JCMA/A126 for the definition of improvement in DR severity level), and (4) proportion of participants with dry retina (defined as CRT <300 μm) as assessed by OCT at weeks 20 and 52. We also examined outcomes relating to treatment burden, such as the proportion of participants who reached disease stability and entered TAE at week 20, proportion of patients who reached the maximum interval at week 52, and mean number of injections.

Overall, safety was assessed through monitoring of adverse events (AEs), physical examinations, vital signs, and clinical safety laboratory tests at prespecified time points. Ocular safety was assessed by ophthalmic examinations (slit lamp, indirect ophthalmoscopy, pre- and 30-minute post-dose intraocular pressure [IOP]) at each study visit. Information from fundus photography and fluorescein angiography was also included.

2.4. Statistical analysis

Statistical analyses were performed using SAS, version 9.3 (SAS Institute). Mean change in BCVA from baseline to week 52 was analyzed in the full analysis set (FAS), which comprised all participants who received study treatment and had a baseline and ≥1 postbaseline BCVA assessment. Analysis on the per protocol set (PPS) included participants in the FAS who completed ≥80% of ideal number of treatments (eight injections) and had no major protocol deviation. Missing data were imputed by the last observation carried forward approach. For participants who received additional treatment (eg, focal laser), post-therapy measurements were imputed using the last observation before therapy. All variables were presented by descriptive statistics. The mean changes in CRT and BCVA from baseline were recorded at each visit up to week 52 and analyzed by paired *t* test. The proportion comparison of participants demonstrating dry retina from baseline to weeks 20 and 52 was analyzed by the McNemar's test. All statistical assessments were performed at the 0.05 level of significance.

Table 1

Baseline demographics and disease characteristics

Characteristic	FAS (n = 45)	PPS (n = 42)
Age, y; mean (SD)	63.7 (8.3)	63.9 (8.1)
Age category, n (%)		
35–49	2 (4)	2 (5)
50–64	24 (53)	22 (52)
65–74	14 (31)	13 (31)
75–83	5 (11)	5 (12)
Sex, n (%)		
Male	28 (62)	26 (62)
Female	17 (38)	16 (38)
T2DM, n (%)	45 (100)	42 (100)
Hemoglobin A1c, %; mean (SD)	7.5 (0.9)[a]	7.5 (0.9)[b]
BCVA, mean (SD), letters	58.3 (11.9)	58.7 (11.6)
CRT, μm; mean (SD)	434.4 (116.8)	437.5 (119.0)

BCVA = best-corrected visual acuity; CRT = central retinal thickness; FAS = full analysis set; PPS = per protocol set; T2DM = type 2 diabetes mellitus.

[a]n = 44 because one participant had missing laboratory data.

[b]n = 41 because one participant had missing laboratory data.

3. RESULTS

3.1. Baseline demographics and disease characteristics

In total, 45 participants were enrolled between August 2015 and November 2017, the mean (SD) age was 63.7 (8.3) years, and 28 participants (62%) were men (Table 1). All participants had T2DM (mean [SD] hemoglobin A1c was 7.5 [0.9]; range, 5.9–9.5). Thirty-nine patients were phakic, and 6 patients were pseudophakic (Supplementary Table 3 http://links.lww.com/JCMA/A126). At baseline, mean (SD) BCVA was 58.3 (11.9) ETDRS letters, and CRT was 434.4 (116.8) μm. Three participants discontinued due to (1) a non–treatment-related cerebrovascular accident, (2) receiving a trans-pars plana vitrectomy (an exclusion criterion violation discovered after enrollment), and (3) an episode of acute pulmonary edema in a patient with DM and hypertension who later experienced full recovery. The last was excluded by the investigator's decision.

3.2. Visual and anatomical outcomes

Overall, improvement in VA (Fig. 1A) and reduction in CRT (Fig. 1B) were noted with the five loading doses before TAE (week 16) and maintained over 52 weeks. Mean (SD) changes in BCVA and CRT were +8.3 (9.3) letters and –138.2 (150.0) μm (both $p < 0.001$) from baseline to week 52. Similar results were observed in the PPS (n = 42), with mean (SD) changes in BCVA

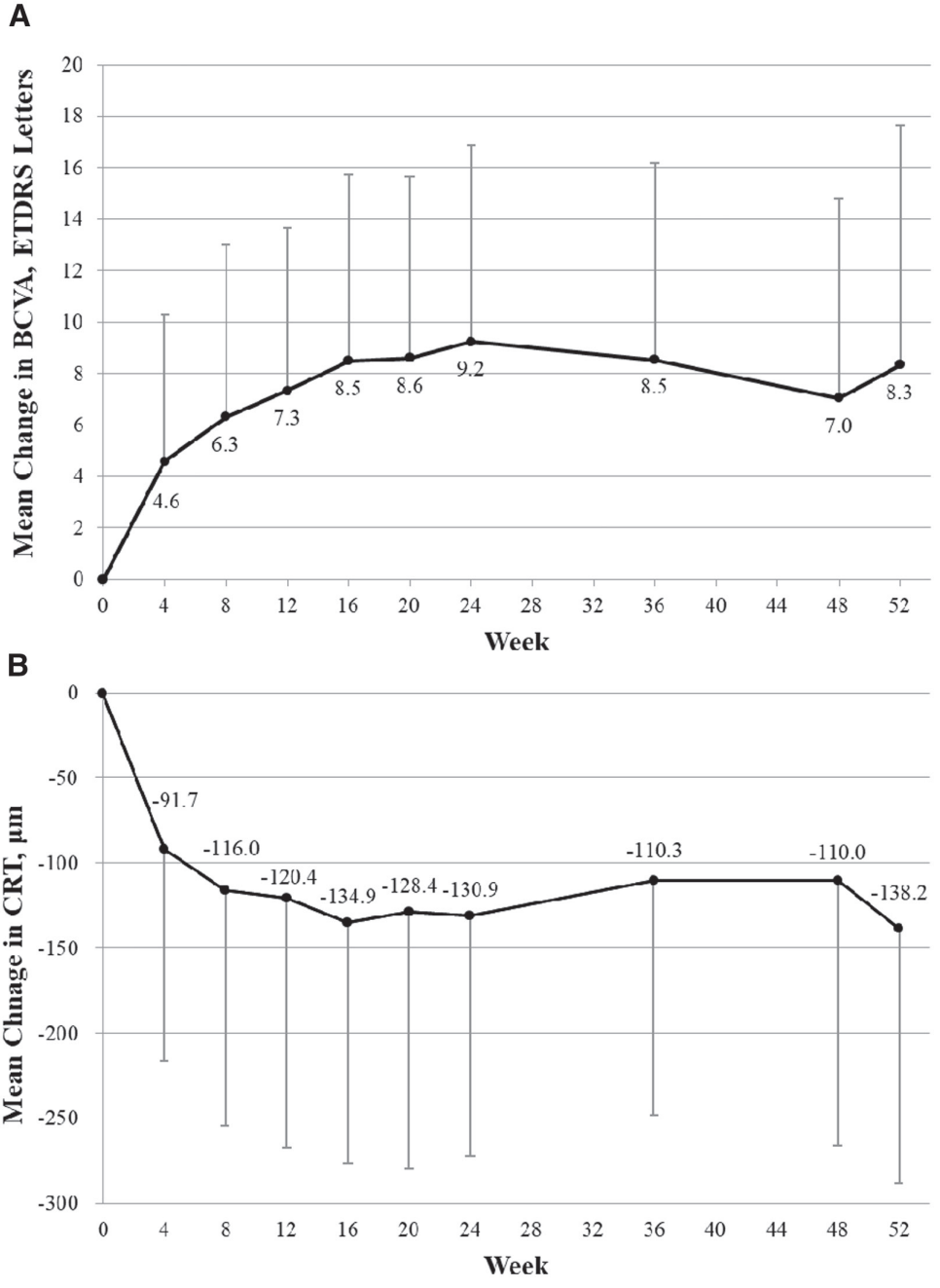

Fig. 1 Visual and anatomical outcomes in the full analysis set (FAS) cohort (n = 45). Mean change in the best-corrected visual acuity (BCVA; A) and central retinal thickness (CRT; B) from baseline to week 52 in FAS. Error bars represent SD. ETDRS = Early Treatment Diabetic Retinopathy Study.

of +9.3 (8.7) letters and mean (SD) changes in CRT of –151.8 (142.1) μm from baseline to week 52.

Table 2 demonstrates 22% (10/45) of participants in the FAS gained ≥15 letters and 14% (6/44) had ≥2-level improvement in DR severity (also see Supplementary Table 4 http://links.lww.com/JCMA/A126 for more information). In addition, the proportion of participants demonstrating dry retina was 44% (18/41) at week 20 and 51% (23/45) at week 52, compared with 13% (6/45) at baseline ($p = 0.002$ and $p < 0.001$). Similar results were found in the PPS.

3.3. Treatment burden outcomes

At week 20, 87% (39/45) of participants achieved disease stability as defined by the criteria and were able to begin extension (Table 2). At week 52, 89% (40/45) reached the maximum injection interval. Over 52 weeks, the mean (SD) number of injections was 7.7 (1.5). In the PPS, more than 90% of participants were able to extend at week 20 and continued to reach the maximum interval at week 52, with mean (SD) of 8.1 (0.2) injections. No supplementary focal or panretinal photocoagulation laser was given to the study eyes after the loading phase of aflibercept during the study period; only one patient received panretinal photocoagulation laser for ocular hypertension in the fellow eye.

3.4. Safety

No serious ocular AEs were reported (Supplementary Table 5 http://links.lww.com/JCMA/A126). The most common drug-related ocular AE was increased IOP (2/45 [4%]), followed by eye pain and eye pruritus (1/45 [2%] for each); all ocular AEs were mild (Table 3). Intravitreal aflibercept was interrupted in one participant because of ocular hypertension in the fellow eye. Nine participants reported serious AEs, none of which were related to the use of aflibercept or protocol-required procedure. All but one had recovered or resolved by the end of treatment. One participant with a history of hypertension, DM, mild mitral regurgitation, and multiple old infarcts experienced dizziness while climbing stairs and sustained a fall during the study period. Brain computed tomography showed old strokes and low-density lesions in the left hemisphere. Further brain magnetic resonance imaging showed recent infarcts in the left pons, deemed unrelated to intravitreal aflibercept treatment or protocol-required procedure by the neurologist and retina specialist. The patient withdrew because of systemic involvement and rehabilitation needs and was reported to have recovered with sequelae.

Overall, ocular abnormalities evaluated by ophthalmic examinations were due to underlying DR, and transient increase (2–3 mm Hg) in IOP post-treatment was noted. Physical examinations did not show clinically significant findings. Laboratory tests showed statistically significant ($p < 0.05$) changes in hemoglobin (–0.7 [1.2] g/dL), hematocrit (–2.0% [3.5%]), red blood cells (–0.2 [0.4] 10^6/μL), and percentage of lymphocyte (–2.2% [7.1%]) at week 52 compared with baseline, but all were determined by investigators to be clinically insignificant. The mean (SD) hemoglobin A1c at week 52 was 7.5% (1.3%), similar to that at baseline (7.5% [0.9%]).

4. DISCUSSION

We reported the outcomes of a 52-week, single-arm, open-label clinical trial using intravitreal aflibercept with TAE regimen for the treatment of DME. Here, patients received five monthly loading doses of 2 mg intravitreal aflibercept injection, followed by a four-week interval extension if disease stability was achieved. With an average 8.1 injections at week 52, mean improvement in BCVA was 9.3 letters; mean decrease in CRT was 151.8 μm in patients who completed >80% of the ideal number of treatments (eight injections PPS). The dosing regimen also led to 22% (10/45) of patients demonstrating ≥15-letter gain and 14% (6/44) showing ≥2-level improvement in DR severity.

Anti-VEGFs have revolutionized DME treatment, with considerable attention now focused on extending treatment interval and individualizing treatment regimens.[12,13] The phase 2 DA VINCI and phase 3 VISTA and VIVID studies of aflibercept in DME supported that an extended follow-up every 2 months (q8w) could yield comparable efficacy to monthly injections.[6,22–25] Patients in the q8w groups among studies had mean

Table 2

Additional outcomes and parameters related to treatment burden

Characteristic	FAS (n = 45)	PPS (n = 42)
Proportion of patients who gained ≥15 ETDRS letters from baseline to week 52, n (%)	10 (22)	10 (24)
Proportion of patients with ≥2-level improvement in DR severity at week 52, n (%)	6/44 (14)	6/42 (14)
Proportion of patients demonstrating dry retina		
Baseline, n (%)	6/45 (13)	6/42 (14)
Week 20, n (%)	18/41 (44)	18/40 (45)
Week 52, n (%)	23/45 (51)	23/42 (55)
Proportion of patients reaching stable disease and entering TAE at week 20, n (%)	39 (87)	39 (93)
Number of injections, mean (SD)	7.7 (1.5)	8.1 (0.2)
Number of injections, median (min, max)	8 (1, 9)	8 (8, 9)
Length of the last injection interval		
12 wk, n (%)	40 (89)	40 (95)
8 wk, n (%)	2 (4)	2 (5)
4 wk, n (%)	3 (7)	0

DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; PPS = per protocol set; TAE = treat and extend.

Table 3

Fifty-two-week safety profile

Characteristics	SAF (n = 45)
Participants with AEs, n (%)	
Any AE	22 (49)
Any TEAE	22 (49)
The most common TEAE (≥4%)	
Pneumonia	3 (7)
Increased IOP	3 (7)
Macular edema (in fellow eye)	2 (4)
Constipation	2 (4)
Bronchitis	2 (4)
Upper respiratory tract infection	2 (4)
Pruritus	2 (4)
Drug-related TEAE (all were mild in severity)	
Increased IOP	2 (4)
Eye pain	1 (2)
Eye pruritus	1 (2)
Any SAE	9 (20)
Any ocular SAE	0
Any nonocular SAE	9 (20)
Any AE leading to discontinuation of the study drug	1
Any AE leading to interruption of the study drug	1
Any death	0

AE = adverse event; IOP = intraocular pressure; SAE = serious adverse event; SAF = safety analysis set; TEAE = treatment-emergent adverse event.

baseline BCVA of 58.8 to 59.4 letters and CRT of 435 to 518 μm. The improvements in BCVA and CRT at 52 weeks were 9.7 to 10.7 letters and 183 to 192 μm, respectively. Regarding treatment burden, an average of 7.2 injections and 0.8 laser treatments were given in the phase 2 DA VINCI study; in phase 3 parallel VIVID/VISTA studies, the number of injections were 8.4/8.7, with additional 1.0/1.5 laser treatments given to 0.7%/8.1% of patients. Recently, the VIBIM study (n = 46) reported clinical results similar to fixed dosing regimen by using a modified aflibercept TAE regimen. Patients with mean baseline BCVA of 56.2 letters and CRT of 489.4 μm showed a visual gain of 9.1 letters and a decrease in CRT by 172 μm with a mean of 8.5 injections at 52 weeks. Over 25% of patients gained >15 letters, and approximately 75% reached the maximum 12-week injection interval.[26] To date, the best evidence comparing the effectiveness of anti-VEGF agents for DME was provided by the DRCR.net Protocol T study.[10,11] With baseline mean BCVA of 64.8 letters and CRT of 412 μm, the BCVA improvement of 13.3 letters and CRT reduction by 169 μm were achieved with a median number of nine intravitreal aflibercept injections during the first year under a protocol-specified PRN regimen with monthly monitoring. The proportion of study eyes that received laser treatment was 37%.[10] In summary, with lower number of visits scheduled for treatment, our study showed similar visual and anatomical outcomes to previous studies with various dosing regimens of intravitreal aflibercept (Table 4). Taiwan's National Health Insurance plan allows for eight doses of anti-VEGF for patients with DME, which is insufficient beyond the first year according to our study, and another 3 to 5 doses are generally needed to maintain VA in years 2 to 3.[10,11]

With due consideration of risk-to-benefit ratio and cost-effectiveness, a TAE regimen attempts to reduce treatment burden and/or uncertainty associated with fixed dosing or PRN (with monthly monitoring) regimens. Given the scarcity of high-quality studies, a general guidance on TAE regimen with anti-VEGFs for DME has yet to be determined.[27] Similar outcomes were reported in the RETAIN and TREX-DME trials of TAE ranibizumab for DME, each of which adopted different dosage conditions (0.5 vs 0.3 mg), initial monthly loading doses (3 vs 4), extension interval (4 vs 2 weeks), extension criteria (investigator-judged VA stability vs algorithm-based percentage change in CRT), and other parameters.[18,19] In RETAIN, the average injection number was 1.7 to 2.1 higher in the TAE groups than in the PRN group over 24 months, whereas a substantial reduction (46%) in clinic visits was observed.[18] In TREX-DME, TAE groups received an average of 2.4 to 3.0 fewer injections compared with monthly dosing.[19] In these two studies, approximately 29% to 44% patients under TAE regimens were able to maintain the maximum 12-week interval.[18,19]

Our extension criteria were simple and practical. Treatment interval was extended by four weeks if participants demonstrated either VA loss of <5 letters since the previous visit or CRT <300 μm. If both VA loss of ≥5 letters and CRT ≥300 μm were met, the next interval was decreased by four weeks. Consequently, the minimum injection number in the first year was eight, and further clinical improvement may be suggested for patients who require additional management. Future studies may be warranted to investigate the effects of applying a criterion that maintains the interval at the current length or one that defines disease stability for at least two consecutive visits before extension.[19,27] Nevertheless, the visual and anatomical outcomes were favorable; 93% (39/42) of patients were able to reach disease stability with the initial five monthly loading injections and begin extension at week 20, with 95% (40/42) achieving the 12-week maximum interval at week 52 in the PPS cohort. These results indicated that our TAE protocol is feasible in routine practice to reduce treatment burden and clinic visits, particularly when poor compliance and/or limited insurance reimbursement may lead to undertreatment in real-world practice.[14,15,17]

Although differences in study design and patient characteristics made it difficult to compare our findings with previous studies, a similar trend in visual and anatomical improvement was still observed. A retrospective cross-trial analysis of nine phase 2 and 3 randomized clinical trials of 0.5 mg ranibizumab and 2 mg aflibercept revealed the mean baseline VA was inversely correlated to VA gains, and mean VA plateaued at approximately 70 (68.5–73.0) letters at 12 months regardless of trial design (agents, regimens, and number of injections).[28] In our PPS cohort, the baseline BCVA was 58.7 letters and the improvement was 9.3 letters, resulting in a final BCVA of 68 letters, which was only 0.5 letters below the lower end of the VA plateau indicated in the cross-trial analysis.[28] Because the efficacy of intravitreal aflibercept was largely maintained beyond one year in previous clinical trials of DME, future studies with larger cohorts are warranted to evaluate the long-term efficacy of the TAE regimen.[6,11,29]

The current study has several limitations. First, because this study lacks dosing comparison groups, the efficacy of TAE aflibercept in DME compared with monthly or PRN regimens remains to be investigated. Second, the limited sample size may

Table 4

Outcomes of selected anti–vascular endothelial growth factor trials for treating diabetic macular edema at 52 wk

Study	Drug, regimen (participants)	Baseline VA, mean (SD) letters	VA change from baseline, mean (SD) letters	Proportion of patients gaining ≥15 letters	CRT change from baseline, μm; mean (SD)	Number of injection[a]	Number of visit schedule for treatment
Current study	Aflibercept, TAE (n = 45)	58.3 (11.9)	+8.3 (9.3)	22%	−138.2 (150.0)	8 (1–9) or 7.7 (1.5)	8 (1–9)
VISTA[24]	Aflibercept, fixed q8w (n = 151)	59.4 (10.9)	+10.7 (8.2)	31%	−183.1 (154)	8.4 (1.3)	9
VIVID[24]	Aflibercept, fixed q8w (n = 135)	58.8 (11.2)	+10.7 (9.3)	33%	−192.4 (150)	8.7 (1.2)	9
DRCR.net protocol T[10]	Aflibercept, PRN (n = 224)	64.8 (11.3)[b]	+13.3 (11.1)	42%	−169 (138)	9 (8–11)	14
DRCR.net protocol T[10]	Ranibizumab, PRN (n = 218)	64.8 (11.3)[b]	+11.2 (9.4)	32%	−147 (134)	10 (8–11)	14
RETAIN[18]	Ranibizumab, TAE without laser (n = 128)	63.9 (10.8)	+6.8 (8.7)	NA	−110 (100)	7 (NA–NA)	≥3 + 9.0 (in 2 y)[c]
RETAIN[18]	Ranibizumab, TAE with laser (n = 121)	61.7 (12.2)	+6.8 (6.9)	NA	−130 (110)	7 (NA–NA)	≥3 + 8.9 (in 2 y)[c]
RETAIN[18]	Ranibizumab, PRN (n = 123)	64.7 (10.2)	7.44 (8.5)	NA	−100 (97)	7 (NA–NA)	≥3 + 16.6 (in 2 y)[c]
TREX-DME[19]	Ranibizumab, TAE (n = 60)	64.1 (NA)	+9.6 (NA)	27%	−146 (NA)	10.7 (NA)	NA

CRT = central retinal thickness; NA = not available; PRN = pro re nata; q8w = every 8 weeks; TAE = treat-and-extend; VA = visual acuity.

[a]Presented as median (range) or mean (SD), when available.

[b]Mean VA of total participants.

[c]Data only available for 24 mo.

have rendered the study underpowered for further subgroup analysis based on baseline VA or CRT, which was conducted in the DRCR.net Protocol T study. Third, our extending criteria focused on disease stability, and the study design assumed five loading doses were sufficient to reach maximal clinical effectiveness. However, some patients may need additional injections before extending to ensure optimal clinical outcome. Lastly, no central reading center was designated for standardized assessment of imaging data; thus, variability among study centers may exist.

In conclusion, this study provided evidence that intravitreal aflibercept injections using a practical TAE protocol in patients with DME resulted in favorable visual and anatomical outcomes at one year. The straightforward extension criteria can be easily applied in practice, thereby reducing treatment burden.

ACKNOWLEDGMENTS

This study was funded by Bayer AG and is registered at clinicaltrials.gov (identifier: NCT04288232; registration date: February 28, 2020). The authors wish to thank all patients who participated in this study.

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