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ORIGINAL ARTICLE

# Aflibercept treatment with treatment-extend regimen in bevacizumab-resistant nAMD: Real-life experience

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## Abstract

**Purpose:** The aim of the study was to evaluate the anatomical and functional effectiveness of the treat-and-extend (TAE) regimen with intravitreal (IV) aflibercept treatment in neovascular age-related macular degeneration (nAMD) patients who responded anatomically poorly after three doses of IV bevacizumab injection.

**Methods:** This observational, single-center, real-life study included adults aged at least 50 years with treatment-naïve nAMD and a best-corrected visual acuity (BCVA) between 25 and 75 Early Treatment of Diabetes Retinopathy Study (ETDRS) letter scores. Three loading doses of IV bevacizumab were administered to all patients, and patients with an anatomical poor response after three loading doses were included in the study. All patients received three doses of IV aflibercept and treatment was continued with the TAE regimen. The primary endpoint was the mean change in BCVA from baseline to week 52.

**Results:** Thirty-six (48.6%) women and 38 (51.4%) men participated in this study, and the average age was 74.4±8.4 years. ETDRS letter gains were 5.5, 9.6, and 13.8 at weeks 12, 24, and 52, respectively. At week 52, a gain of 15 letters or more was detected in 34 of the patients (45.9%). The anatomical gains were 72.3 µm, 94.3 µm, and 116.7 µm at 12, 24, and 52 weeks, respectively. The mean number of injections performed was 8.2. The mean final interval was 8.8 weeks. The proportion of patients with 12 weeks or more between treatments was 16/74 (21.6%).

**Conclusion:** In treatment-naïve nAMD patients refractory to bevacizumab, IV aflibercept administered using the TAE regimen improved and maintained functional and anatomical outcomes for 52 weeks.

**Keywords:** Aflibercept; age-related macular degeneration; resistant; treat-extend.

Age-related macular degeneration (AMD) is the leading cause of vision loss.[1] Advanced AMD is classified into a non-exudative or atrophic form and an exudative or neovascular form.[2] The development and approval of intravitreal (IV) anti-VEGF therapy in 2006 revolutionized the treatment of neovascular AMD (nAMD).[3] Treatment of nAMD consists of administration of anti-VEGF agents such as bevacizumab, aflibercept, and ranibizumab.[3-5]

Fixed-monthly therapy was the first dosing regimen approved for anti-VEGF therapy, based on the results of multiple pivotal Phase III clinical trials.[5,6] However, there was a need to develop different treatment regimens due to the high number of recurrent control visits and the burden of the number of injections on both patients, physicians and the health-care system. These days, clinicians often practice a reactive pro re nata (PRN) regimen, in which patients are monitored with regular visits and treated based on signs of disease activity, or a proactive treat-and-extend (TAE) regimen, which allows gradual increases in treatment intervals based on disease activity. Although the best visual results are achieved with consistent monthly dosing, less frequent dosing has been shown to effectively reduce

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retinal thickness and improve vision.[7-11] In the PRN regimen, the number of anti-VEGF injections is minimized because the anti-VEGF agent is administered only when signs of disease activity are observed. However, regular monthly visits are often a burden for both patients and treating physicians. In contrast, the TAE regimen was developed to achieve the treatment benefit of anti-VEGF while reducing the number of visits. The TAE approach is a personalized dosing schedule that allows for gradual increases in treatment intervals to determine the longest possible interval without disease recurrence. The TAE regimen begins with 3–5 loading doses per month to find the maximum injection interval for each patient, while macular thickness is monitored through optical coherence tomography (OCT) and intervals are extended by 2 weeks or 1 month. When the patient has the longest intervals, fixed interval injections are applied to the patient.

The TREX-AMD, CANTREAT, and TREND randomized clinical trials investigated the TAE treatment regimen with IV ranibizumab and achieved results comparable to fixed dosing.[9-11] The TAE regimen with IV aflibercept was investigated in the ARIES, ALTAIR studies, and the randomized clinical trials of Haga et al.[7,8,12] This study aims to evaluate the effectiveness of the TAE regimen with IV aflibercept treatment in patients with an anatomical poor response after 3 doses of IV bevacizumab injection and to compare it with pivotal studies in the literature. To the authors' best knowledge, the current study is the first to evaluate a TAE regimen in patients refractory to IV bevacizumab who were switched to IV aflibercept therapy.

## Materials and Methods

### Study Design and Patients

This retrospective, single-center, observational study included 74 eyes of 74 treatment-naïve patients with nAMD. According to the treatment protocol, three loading doses of IV bevacizumab injections were administered to all patients, and patients with an anatomical poor response after three loading doses were included in the study. All patients received three doses of IV aflibercept injections after three bevacizumab injections, and treatment was continued with the TAE regimen.

All procedures were performed following the principles of the Declaration of Helsinki. Institutional review board approval was obtained from the Local Ethics Committee (IRB:2023-KAEK-91). Informed consent was obtained from all patients.

### Inclusion and Exclusion Criteria

Adults over the age of 50, with exudative changes due to macular neovascularization lesions secondary to AMD, proven by fundus fluorescein angiography (FFA), and with a best-corrected visual acuity (BCVA) Early Treatment of Diabetes Retinopathy Study (ETDRS) letter score between 24 and 72 were included in the study. As in previous pivotal studies, in order not to affect the results of the study, patients with baseline vision level of 24–72 letters, excluding patients with very poor or good vision, were included in the study.[6,9,13] One eye was considered a working eye. If both eyes were suitable, the eye with worse VA was selected as the study eye.

The main exclusion criteria were as follows: (1) Previous intraocular anti-VEGF use, (2) retinal diseases other than nAMD, (3) previous intra/periocular steroid use, (4) history of vitreo-retinal surgery in the study eye, (5) previous or active inflammatory ocular pathologies such as uveitis, and (6) corneal and/or lens opacities that may affect OCT imaging.

### Treatment and Assessment Schedule

Initially, data such as the patient's age and gender were recorded. Ophthalmological examination, including anteroposterior segment slit lamp biomicroscopy as well as visual acuity and ETDRS letter score, non-contact air tonometry intraocular pressure (IOP) measurements, was performed at all visits. Color fundus photography and spectral domain OCT were performed at each visit.

Colored fundus and FFA images were used to determine fundus angiographic features (TRC-50DX, Topcon Corporation, Tokyo, Japan). OCT scanning (Cirrus HD-OCT 5000, Carl Zeiss Meditec AG, Jena, Germany) was used to determine central macular subfield thickness (CMST) and accompanying exudative nAMD features. Those with OCT signal strength above 7/10 were included in the study. The foveal center in the OCT fundus image was identified using the automatic foveal localization algorithm. The examination protocol consisted of a $6 \times 6$ mm macular cube centered on the fovea, consisting of 128 horizontal b-scans of 512 a-scans each. Retinal thickness values for each of the nine areas corresponding to ETDRS were automatically calculated by Cirrus OCT software. Cirrus OCT's Macular Thickness Analysis software uses the internal limiting membrane (ILM) and the posterior portion of the retinal pigment epithelium (RPE) as reference layers for central macular thickness analyses. The layer lines were checked for errors, and if errors were present, the ILM and RPE layer lines were manually corrected by the researchers.

Patients in all groups were initially administered 1.25 mg IV bevacizumab injection as a loading dose. The insurance policy required nAMD patients to receive three doses of bevacizumab injections as initial treatment. Similar

to previous studies, patients with persistent intraretinal and/or subretinal fluid or drop in vision after 3 months of monthly bevacizumab injection were considered refractory to treatment and switched to aflibercept therapy.[14-16] Patients who switched to aflibercept treatment were administered 3 consecutive monthly aflibercept injections as an aflibercept loading dose. After IV aflibercept therapy was administered, patients continued aflibercept therapy with the TAE regimen.

### TAE Protocol

The eyes of those in the treatment TAE protocol group received three consecutive IV injections of 1.25 mg bevacizumab and 2 mg aflibercept every 4 weeks during the "loading phase," followed by a TAE regimen. The treatment interval between injections was extended or shortened by 2 weeks depending on disease activity on OCT and BCVA assessment. After the loading phase of aflibercept, patients could extend their follow-up and treatment visits if they had no disease activity on OCT images and the BCVA was either improved or stable compared to that at the last visit. No BCVA loss ≥5 letters defined as stability. Disease activity by OCT was determined based on any new intraretinal/subretinal fluid or hemorrhage or neovascularization. The follow-up interval was extended by 2 weeks each time, starting from 2 weeks at baseline. The longest allowed follow-up interval was 16 weeks. An injection was administered at each visit. The follow-up interval was shortened by 2 weeks if OCT revealed new disease activity. In the TAE regimen, if CMST remained stable for two consecutive sessions, visual stabilization continued, and the interval between sessions was extended to a maximum of 16 weeks, treatment was postponed and the next interval was shortened to 8 weeks. If there was no worsening of nAMD, the patient was monitored without treatment at 8-week intervals.

### Outcome Measures

The primary outcome measure was changes in ETDRS letter score at 52 weeks, and secondary outcomes included various parameters (CMST changes, number of injections, mean interval between injections, proportion of eyes achieving a gain of 15 letters). This report presents early results at 52 weeks.

### Statistical Analysis

Statistical analysis was performed using SPSS software, version 22.0 (IBM SPSS, Chicago, IL, USA). All parameters were analyzed for distribution by the Shapiro–Wilk test for normality analysis. Descriptive statistical methods, including percentage and mean±standard deviation or median (IQR) values, were used to present the baseline characteristics of data according to the normality of distribution. The categorical variables were analyzed using the Chi-square test. The variations in parameters were tested for significance using the Wilcoxon signed ranks test in a non-normal distribution and paired sample t-test in a normal distribution for consecutive measurements. While evaluating the difference of the BCVA and CMST values at different time points of the groups, the repeated measurement analysis was used. The evaluations were made at the 95% confidence interval, and the $p<0.05$ was a statistically significant difference.

## Results

### Patient Demographics and Baseline Characteristics

Thirty-six (48.6%) women and 38 (51.4%) men participated in this study, and the average age was 74.4±8.4 years. Seventy-four eyes of 74 treatment-naïve patients were included in the study. Sixty-two (83.8%) of the patients were phakic and 12 (16.2%) were pseudophakic. Baseline CMST, ETDRS letter score, and IOP were 392.3±32.8, 42.9±16.9, and 14.6±2.9, respectively. Baseline patient demographics and ocular characteristics are shown in Table 1.

### Functional and Anatomical Outcomes

#### BCVA

The BCVA ETDRS letter score of the study group was 42.9±16.9, 48.5±17.9, 52.5±17.8, and 56.8±15.1 at the baseline, 12-, 24-, and 52-weeks visits, respectively (Table 2 and Fig. 1). ETDRS letter gains were 5.5±11.4, 9.6±13.9 and 13.8±14.2 at weeks 12, 24 and 52, respectively (Table 3 and

**Table 1.** Baseline patient demographics and baseline ocular characteristics

| Characteristic | Study group (n=4) |
|---|---|
| Mean age±SD, years | 74.4±8.4 |
| Gender, n (%) | |
| Female | 36 (48.6) |
| Male | 38 (51.4) |
| Lens status | |
| Phakic, n (%) | 62 (83.8) |
| Pseudophakic, n (%) | 12 (16.2) |
| Mean CMST±SD, µm | 392.3±32.8 |
| Mean BCVA±SD (letters) | 42.9±16.9 |
| IOP±SD mmHG | 14.6±2.9 |

SD: Standard deviation; BCVA: Best-corrected visual acuity; CMST: Central macular subfield thickness; ETDRS: Early treatment diabetic retinopathy study; IOP: Intraocular pressure.

**Table 2.** Changes in best-corrected visual acuity, central macular subfield thickness and intraocular pressure during the study

| | TAE aflibercept n=30 | p[a] |
|---|---|---|
| BCVA (ETDRS letters)±SD (letters) | | |
| Baseline | 42.9±16.9 | |
| 12th week | 48.5±17.9 | <0.001 |
| 24th week | 52.5±17.8 | <0.001 |
| 52th week | 56.8±15.1 | <0.001 |
| CMST±SD, µm | | |
| Baseline | 392.3±32.8 | |
| 12th week | 320.1±32.5 | <0.001 |
| 24th week | 298±33.2 | <0.001 |
| 52th week | 275.7±27.8 | <0.001 |
| IOP±SD, mm HG | | |
| Baseline | 14.6±2.9 | |
| 12th week | 14.5±2.7 | 0.577 |
| 24th week | 14.5±2.4 | 0.681 |
| 52th week | 14.8±2.6 | 0.610 |

SD: Standard deviation; BCVA: Best-corrected visual acuity; CMST: Central macular subfield thickness; ETDRS: Early treatment diabetic retinopathy study; TAE: Treat-and-extend; IOP: Intraocular pressure. P<0.05 was considered statistically significant in 95% confidence interval (comparisons between baseline and other visits). [a]Paired sample t-test.

Fig. 1). Statistically significant visual gains were detected at all visits compared to baseline (p<0.001 for each). At week 52, a gain of 15 letters or more was detected in 34 of the patients (45.9%).

## CMST

CMST values of the study group were 392.3±32.8 µm, 320.1±32.5 µm, 298±33.2 µm, and 275.7±27.8 µm at the baseline, 12-, 24-, and 52-week visits, respectively (Table 2 and Fig. 1). The anatomical gains according to the change in CMST were 72.3±20.5 µm, 94.3±31.1 µm and 116.7±31.9 µm at 12, 24 and 52 weeks, respectively (Table 3 and Fig. 1). Statistically significant anatomical gain was detected at all visits compared to baseline (p<0.001 for each).

## Treatment Exposure

The mean number of injections performed in the study group during the 52-week follow-up was 8.2±2.5 (Table 3). The mean final treatment interval was 8.8±2.4 weeks. At week 52, the proportion of patients with 12 weeks or more

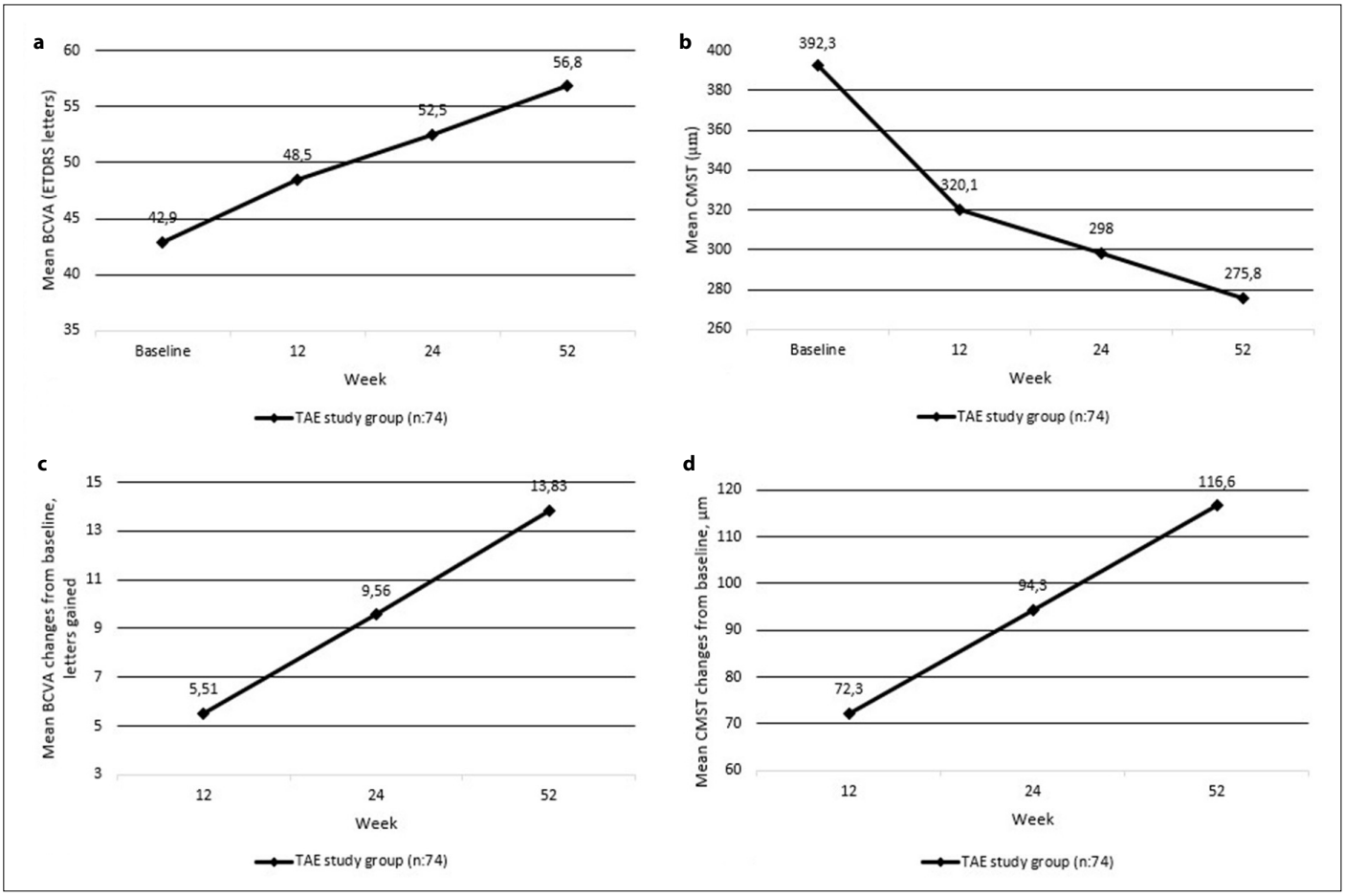


**Fig. 1.** Changes in mean BCVA ETDRS letters and CMST values compared to baseline at the 12th week, 24th week and 52nd week. (a) Mean BCVA ETDRS letters change chart (b) Mean CMST chart (c) Mean BCVA ETDRS letters gains chart (d) Mean anatomical gains changes from baseline. BCVA: Best-corrected visual acuity, CMST: Central macular subfield thickness, ETDRS: Early treatment diabetic retinopathy study, TAE: Treat-and-extend

**Table 3.** Differences in BCVA and CMST values compared to baseline and treatment exposure data

| | TAE aflibercept n=30 |
|---|---|
| BCVA changes (ETDRS letters) | |
| 12th week | 5.51±11.4 |
| 24th week | 9.6±13.9 |
| 52th week | 13.8±14.2 |
| CMST changes (µm) | |
| 12th week | 72.3±20.5 |
| 24th week | 94.3±31.1 |
| 52th week | 116.7±31.9 |
| Number of injections | 8.2±2.5 |
| Last extension week | 8.8±2.4 |

BCVA: Best-corrected visual acuity; CMST: Central macular subfield thickness; ETDRS: Early treatment diabetic retinopathy study; TAE: Treat-and-extend.

between treatments was 16/74 (21.6%). No significant change was detected in IOP values between visits.

No major ophthalmological (endophthalmitis, vitreous hemorrhage, retinal detachment, uveitis) adverse effects were observed during the 12-month follow-up. No systemic adverse effects were observed in any patient during follow-up.

## Discussion

The current study investigated the effectiveness of TAE in the treatment of nAMD using IV aflibercept in bevacizumab-refractory patients. Early results at 52 weeks showed a gain of 13.8 letters with an average number of injections of 8.2. About 45.9% of patients had a gain of 15 or more ETDRS letters. Anatomical gain at 52 weeks averaged 116.7 µm, and none of the eyes showed an increase in CMST from baseline. At week 52, the proportion of patients with 12 weeks or more between treatments was 16/74 (21.6%).

VIEW1 and VIEW2 studies are two parallel Phase 3 pivotal randomized clinical trials that demonstrated the effectiveness of a fixed-dose regimen using aflibercept in the treatment of nAMD.[6,13] After these studies, aflibercept was approved for the treatment of nAMD. These double-masked, multicenter, parallel-group, active-controlled studies included 2419 treatment-naïve patients with nAMD. Patients were randomized 1:1:1:1: aflibercept 0.5 mg every 4 weeks (0.5q4); 2 mg aflibercept (2q4) every 4 weeks; 2 mg aflibercept every 8 weeks (2q8) after 3 injections at weeks 0, 4, and 8; or 0.5 mg ranibizumab every 4 weeks. According to the results of the 52nd week, an average improvement of +8.7 letters (0.5 mg/q4 ranibizumab) was observed in the control group, while in the aflibercept groups, an improvement of +9.3 letters in the 2q4 group, +8.4 letters in the 2q8 group, and +8,.3 letters in the 05q4 group was observed. All aflibercept and ranibizumab groups were equally effective in improving BCVA and preventing BCVA loss at 96 weeks, according to the study, which presented the 96-week results of the VIEW1 and VIEW2 study.[13] However, it is difficult to maintain a fixed dose regimen in clinical practice and real life because repeating injections every 1 or 2 months can become a burden for patients, doctors, and the health-care system. In addition, most patients with nAMD treated with anti-VEGF with the TAE regimen achieved visual stability with less treatment at year 2.[7-9] Because nAMD appears to be stabilized with adequate treatment, there is a potential risk of overtreatment with a fixed-dose regimen.

According to the results of the randomized controlled ALTAIR study, which compared IV aflibercept treatment with TAE regimens (2-week or 4-week extension interval), visual gain at week 52 was +9 and +8.4 letters in the 2- and 4-week extension groups, respectively.[7] According to the 96-week results of this study, letter gains were +7.6 and 6.1 letters. The randomized, open-label, Phase 3b/4 ARIES trial evaluated whether early-onset TAE with IV aflibercept treatment was lower than late-onset TAE.[8] In the results of this study at 104 weeks, a gain of +8.4 letters compared to baseline was observed in the early TAE group, while a gain of +11.9 letters was observed in the late TAE group. From baseline to week 104, 93.4% and 96.2% of patients maintained their BCVA. According to the 52nd week results of the prospective, randomized controlled, multicenter TREX-AMD study, which compared IV ranibizumab treatment with monthly fixed dose regimen and TAE regimen, a gain of +10.5 and +8.7 letters was achieved with the fixed dose and TAE regimen, respectively (p=0.64).[9] According to the results of this study, the TAE regimen was comparable to the fixed-dose regimen in terms of vision gains. In the current study, early results at 52 weeks showed a gain of +13.8 letters with the TAE regimen, and similar and comparable vision gains were achieved when compared with the fixed-dose regimen and the studies investigating the TAE regimen mentioned above.

In the ALTAIR study, the proportion of patients with a gain of at least 15 ETDRS letters at week 52 was 32.5% and 30.9% in the 2-week and 4-week extension interval groups, respectively.[7] At the 96th week, these values were 28.5% and 31.7%, respectively. In the ARIES study, the proportion of patients with a gain of 15 ETDRS letters from baseline to weeks 52 and 104 was 19.8% and 18.9% in the early TAE arm and 27.9% and 22.1% in the late TAE arm.[8] In the TREX-AMD study, 20% of patients in the monthly dosing regimen

group and 30% of patients in the TAE group gained at least 15 ETDRS letters at month 24.[9] According to our early results at week 52, the proportion of patients with a gain of 15 or more letters was slightly higher compared to the studies mentioned above. The reason for this may be that, while in the pivotal studies where the above-mentioned TAE regimen was investigated, a monthly loading dose of anti-VEGF injection was administered for 3 months, whereas in the current study, six IV anti-VEGF injections were administered with bevacizumab-aflibercept, including three loading doses each. This may be due to the fact that we achieved more effective VEGF inhibition in the early stages of the treatment of the disease with a higher number of injection loading doses.

In the 52nd week results of the VIEW1 study, there was a change in central retinal thickness of −116.8, −116.5, −115.6, and −128.5 μm in the control, 2q4, 05q4, and 2q8 groups, respectively.[6] In the VIEW2 study, these values were −138.5, −156.8, −129.8, and −149.2 μm, respectively.[6] In the ALTAIR study, the mean change in central retinal thickness in the 2-week and 4-week interval groups, respectively, was −134.4 μm and −126.1 μm (week 52) and −130.5 μm and −125.3 μm (week 96).[7] In the ARIES study, the mean central retinal thickness change from baseline to week 104 in the early and late TAE groups was −135.6 μm and −125.1 μm, respectively.[8] In the TREX-AMD study, an anatomical gain of mean −170 μm was achieved in both the monthly and TAE groups at 24 months.[9] In the current study, the anatomical gain according to the change in CMST at week 52 was 116.7 μm. Our anatomical gain results were similar and comparable to those of the VIEW1/2, ALTAIR, and ARIES studies. However, it was lower than the TREX-AMD study. This may be because the baseline central retinal thickness values of the patients included in this study were higher than the baseline values of the current study and other studies mentioned above (TREX-AMD baseline central retinal thickness value was 511 μm, while in the current study this value was 392 μm).

In the ALTAIR study, the average number of injections performed at 52 weeks was 7.2 and 6.9 in the 2-week and 4-week interval groups, respectively.[7] In the ARIES study, the mean number of injections at 52 weeks was 7.1 and 8 in the early and late TAE groups, respectively.[8] In the TREX-AMD study, 13 injections were made with a fixed dose regimen in 52 weeks, while an average of 10.1 injections were made in the TAE group.[9] In the current study, the average number of injections administered over 52 weeks was 8.2. Our mean number of injections data at 52 weeks was consistent with other studies. In the ALTAIR study, the number of additional injections in the 2-week and 4-week interval groups between 52 and 96 weeks were 3.6 and 3.7, respectively. In the ARIES study, the number of additional injections between 52 and 104 weeks were 4.9 and 5 in the early and late TAE groups, respectively. In these studies, the number of injections in the 2nd year decreased as expected in the TAE regimen. According to the results of the TREX-AMD study, visual and anatomical gains comparable to the fixed dose regimen were achieved with the TAE regimen with fewer injections.[9] The current study presents early results at 52 weeks, and we believe that the reduction in treatment frequency will be significant in the 2-year results. Even according to our early results, we achieved visual and anatomical gains comparable to pivotal fixed monthly-dose regimens with a lower number of injections, with an average of 8.2 injections.[6]

In the ALTAIR study, the mean final treatment interval at 52 weeks was 10.7 and 11.8 weeks in the 2-week and 4-week interval groups, respectively.[7] Based on the 104-week results in the ARIES study, the mean final treatment interval was 11.5 and 11.4 weeks in the early and late TAE groups, respectively.[8] In the TREX-AMD trial, at 24 months, 37% of patients in the TAE group were on an extension interval of 11 or 12 weeks, and the mean maximum tolerated extension interval was 8.5 weeks.[9] In the current study, the average final treatment interval was 8.8 weeks at 52 weeks. At 52 weeks, the proportion of patients with a treatment interval of 12 weeks or more was 21.6%. Mean final treatment interval data were modestly lower than other studies. The reason for this may be that, while in the above-mentioned studies, the TAE regimen was switched after 3 loadings, in the current study, the TAE regimen could only be switched after 6 months of monthly anti-VEGF loading and the treatment duration with the TAE regimen was shorter.

Our study had several limitations. It was a single-arm study without a control group. It evaluated patients who were switched from bevacizumab treatment rather than the effectiveness of a single type of anti-VEGF. The number of cases was relatively small compared with pivotal studies. However, to the authors' best knowledge, the current study is the first to evaluate a TAE regimen in patients refractory to IV bevacizumab who were switched to IV aflibercept therapy. Two-year results are needed to reveal the difference in TAE in the number of injections, number of visits, and extension intervals.

## Conclusion

According to early results of this real-life study, IV aflibercept administered to treatment-naive nAMD patients with treatment intervals of 2 weeks and a maximum treatment interval of 16 weeks using the TAE regimen in those refractories to bevacizumab improved and maintained functional and anatomical outcomes for 52 weeks. At the same time, no complications were observed and the burden of the patients was reduced with the more flexible treatment regimen. Visual and anatomical results were achieved with the IV aflibercept TAE regimen in bevacizumab-resistant patients, comparable to the results of the pivotal fixed-dose regimen and TAE regimen studies.

**Ethics Committee 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 Kastamonu University Clinical Research Ethics Committee (IRB number: 2023-KAEK-91).

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