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RETINAL DISORDERS

Treat-and-extend versus fixed bimonthly treatment regimens for treatment-naive neovascular age–related macular degeneration: real world data from the Fight Retinal Blindness registry

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Abstract

Purpose To compare the outcomes of two different antivascular endothelial growth factor treatment regimens for treatment-naive eyes with neovascular age-related macular degeneration in routine clinical care at 12 and 24 months in Spain.

Methods Observational study using the Fight Retinal Blindness (FRB) outcomes registry platform. Eyes were treated with fixed bimonthly (FB) aflibercept group at one center and a treat-and-extend (TAE) regimen using either aflibercept or ranibizumab at the other center.

Results We included 192 eyes. Of these, 160 eyes (83%) completed 12 months (86 TAE and 74 FB) and 79 (41%) completed 24 months (46 for TAE and 33 for FB) of follow-up. No statistically significant differences ($p > 0.05$) were found regarding mean visual acuity (VA, logMAR letters) at baseline (12 month cohort TAE 59.6 vs FB 57.9; 24 month cohort TAE 61.7 vs FB 62.6), final mean VA (12 month cohort TAE 61.1 vs FB 63.0; 24 month cohort TAE 64.8 vs FB 66.4), and median number of injections (12 months TAE 7 vs FB 7; 24 months TAE 11 vs FB 12). However, the distribution of injection frequencies for the TAE group was larger, with 35% of TAE eyes receiving ≤ 6 injections at 12 months compared with only 19% of FB eyes ($p = 0.024$).

Conclusion Similar VA results were observed with TAE and FB regimens, with no differences in the median number of injections. However, the TAE approach seemed to deliver a wider distribution of injection frequencies due to its individualized approach, which may help reduce the burden of injections in some eyes.

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Key messages

- According to several clinical trials, a treat-and-extend (TAE) intravitreal anti-VEGF approach to neovascular age-related macular degeneration (nAMD) can deliver similar visual acuity (VA) results as fixed regimens. Whether this also occurs in the real-world is of great practical interest.
- We found that TAE and fixed-bimonthly anti-VEGF regimens for nAMD provided similar VA outcomes in an uncontrolled observational setting.
- Treat-and-extend seemed to deliver a more individualized approach with a wider distribution of injection frequencies, which may help reduce the burden of injections in some eyes.

Keywords Neovascular age–related macular degeneration · Treat and extend · Fixed bimonthly · Electronic medical record · Benchmark standard · Naive

Introduction

Neovascular age–related macular degeneration (nAMD) is currently the leading cause of legal blindness in adults over 65 years old in most developed societies [1–3]. Intravitreal injection of antivascular endothelial growth factor (VEGF) agents is the gold-standard treatment for nAMD [2, 4–6]. Contrary to clinical trial scenarios, the exponentially growing activity burden related to an increasing prevalence of nAMD cases represents a significant challenge for retina departments worldwide nowadays. Different treatment strategies have been proposed to reduce the treatment burden associated to nAMD management in the real world, since the pivotal clinical trials of intravitreal therapy for nAMD used mainly fixed dosing intervals, either monthly or bimonthly [4–6].

The *pro-re-nata* (PRN) strategy, proposed by the PrONTO study in 2007, consisted of monthly visits with injections given only when lesions were active, mainly assessed by optical coherence tomography (OCT). Whereas visual outcomes were comparable to those achieved with monthly injections, the need for monthly monitoring made this approach difficult to implement in routine clinical care so more proactive regimens were increasingly adopted [7–9].

Treat and extend (TAE) [10–12] is a proactive treatment regimen in which treatment is administered in each visit, but the treatment intervals change depending on the CNV activity: if the lesion is inactive, treatment intervals are extended typically by 2 weeks; if, conversely, the lesion is active, treatment intervals are reduced, e.g., by 2 weeks. Strong clinical evidence of each regimen's advantages and disadvantages is now widely known [13–17]. In general, variable treatment interval approaches appear to yield visual acuity outcomes that are not inferior to fixed interval regimens with fewer injections [11, 18, 19]. In nAMD, this real world data is particularly important given that high treatment burden could potentially prevent outcomes of routine clinical care to achieve those observed in clinical trials, which cannot be effectively generalized [14, 20].

Despite the importance of observational studies of treatment outcomes in real world practice, the vast majority of observational reports on nAMD outcomes focus on the results of a single treatment regimen, with very few real world studies that have compared different treatment strategies. With this aim in mind, we set up an observational comparative study of outcomes of a fixed regimen (bimonthly aflibercept) versus a TAE regimen in naive nAMD eyes at 12 and 24 months using the Fight Retinal Blindness (FRB) online outcomes registry software [21].

Materials and methods

Study design

This was a database observational study of treatment-naive nAMD eyes that had undergone antiVEGF intravitreal therapy according to routine clinical care in two sites in Spain and had been tracked using the FRB system online tool [21]. Both study sites belong to the same ophthalmology service (Institut Clinic of Ophthalmology, Hospital Clínic of Barcelona, Barcelona, Spain) acting in two different outreaches (Maternitat: site A; Sagrat Cor: site B) operating with different treatment regimens due to logistic and site-specific reasons. The FRB system is a prospectively designed observational web–based registry that collects data from each clinical visit including visual acuity (VA) notation as minimum angle of resolution (logMAR) letters (best of uncorrected, corrected or pinhole visual acuity), choroidal neovascular (CNV) lesion activity presence in each visit—intraretinal or subretinal fluid by OCT or hemorrhage by funduscopy—intravitreal treatment (IVT) and associated ocular adverse events. Treatment decisions and visit schedules were driven by real world site

procedures and routine clinical care. Institutional review board and ethics committee approvals were obtained from both study sites, and all study participants provided written informed consent.

Study population and outcome measures

Treatment-naive nAMD eyes tracked in the FRB registry between March 2015 and June 2019 were included in the study. Eyes completing a minimum follow-up of 12 months were analyzed, with an additional analysis of eyes that completed 24 months of treatment. Two independent IVT units of the same tertiary referral ophthalmology service participated in the study, with different treatment regimens selected at physician discretion. One site used fixed bimonthly (FB) aflibercept and the other site followed a TAE approach with either aflibercept or ranibizumab. The fixed aflibercept regimen consisted in 3 monthly injections as a loading dose followed by FB dosing during the first 12 months; then, if the CNV was inactive, the dosing interval changed to every 3 months, which could be shortened back to bimonthly if the CNV reactivated. The other site followed a standard TAE approach using either aflibercept or ranibizumab after a loading dose of 3 monthly injections. The TAE site carried out IVT at the time of the clinical evaluation whereas the FB site performed IVT in the following 7 days because of drug availability within the pharmacy department of that site. The primary outcome measure was final VA at 12 and 24 months for the eyes that completed these follow-up periods. Secondary outcomes were VA change from baseline, number of injections, number of visits and proportion of eyes maintained on different treatment intervals (i.e., ≤ 4 weeks, 5–6 weeks, 7–8 weeks, 9–10 weeks, 11–12 weeks, and ≥ 13 weeks).

Statistical analysis

Absolute frequencies and percentages (%) were used to describe categorical variables as well as overall number of eyes in each treatment interval. Description of quantitative variables was performed with mean and standard deviation (SD), median (first and third quartiles [Q1, Q3]), and 95% confidence interval (CI) where appropriate. Student's *t*, Wilcoxon rank-sum, ANOVA, and chi-square tests were used as appropriate to compare baseline characteristics between site groups for 12- and 24-month completers. Visual acuity outcomes over 12 and 24 months were assessed using longitudinal generalized additive models. Longitudinal models included all available visit data from completers and noncompleters and were adjusted for age and VA at baseline and intrapatient correlation. The resulting adjusted estimates of VA were calculated for both groups assuming equal age and VA at baseline set at the sample mean of the overall cohort. Negative binomial regression adjusted for age and VA at baseline, and intrapatient correlation was used to compare injections and visits. A bilateral type I error of 5% was established. All analyses were performed using R version 3.6.1.

Results

Recorded data included 192 treatment-naive nAMD eyes receiving antiVEGF therapy eyes under either FB (site A) or TAE (site B), with no significant differences in gender distribution, mean age and mean baseline VA (Table 1). Once inclusion criteria were applied, outcomes were analyzed for 160 eyes (86 for the TAE and 74 for the FB site) that were followed for at least 12 months, of which 79 eyes also completed a 24-month follow-up period (46 for site TAE and 33 for site FB). No statistically significant differences were found for baseline VA (logMAR letter score) in the 1-year group (mean [SD] TAE 59.6 [17.1] vs FB 57.9 [16.5], $p = 0.545$) and the 2-year group (TAE 61.7 [15.1] vs FB 62.6 [14.6], $p = 0.786$) (Tables 2 and 3).

Regarding functional outcomes, VA change (adjusted by age and baseline VA) and final VA were analyzed. No statistically differences between treatment regimens at 12 months were found in VA change (mean [95% CI] TAE + 0.5 [− 2.1, + 3.5] vs FB + 5.2 [+ 2.2, + 8.3], $p = 0.104$) or final mean VA (TAE 61.1 [20.0] vs FB 63.0 [16.5], $p = 0.513$) (Table 2, Fig. 1). Considering the 24-month group, no differences were found in either VA change (mean [95% CI] TAE − 0.1 [− 3.2, + 3.0] vs FB + 3.6 [− 1.3, + 8.6], $p = 0.931$) or final mean VA (TAE 64.8 [15.4] vs FB 66.4 [16.2], $p = 0.319$) (Table 3, Fig. 1).

Site A (FB) cases were predominantly treated with aflibercept whereas site B (TAE) used aflibercept in approximately 60% and ranibizumab in 40% of cases, maintaining this distribution at both 12- and 24-month timepoints. No differences were found in the proportion of active lesions between FB and TAE cases at 1 year (56% vs 47%; $p = 0.262$) and two years (47% vs 48%; $p = 0.954$) (Tables 2 and 3). The median number of injections at 12 months (TAE 7 vs FB 7, $p = 0.410$) and 24 months (TAE 11 vs FB 12, $p = 0.742$) was similar for both treatment regimens. However, the distribution of injection frequency (Fig. 2) for the TAE group was wider, with 35% of TAE eyes receiving ≤ 6 injections at 12 months compared with only 19% of FB eyes ($p = 0.024$). Similarly, at 24 months, 39% of TAE eyes received ≤ 10 injections compared with 15% in the FB group ($p = 0.021$). There were also more eyes in the TAE group that had a treatment interval of at least 12 weeks by the end of the first year compared with eyes in the FB group (42% vs. 25%, respectively, $p = 0.032$).

Finally, a subgroup descriptive analysis between 12-month follow-up completers and noncompleters of possible differences in gender, age, and baseline VA between was also undertaken (Table 4). Compared to the completers group, the noncompleters group was found to have a lower proportion

Table 1 Demographics partitioned by treatment regimens

	All Eyes	Treat-and-extend	Fixed bimonthly	*p* value
Eyes	192	102	90	
Patients	165	94	71	
Females, % patients	63.0%	64.9%	60.6%	0.684
Age, mean (SD)	81.8 (7.3)	82.8 (7.0)	80.7 (7.5)	0.044
Baseline VA				
Mean (SD)	58.0 (17.6)	58.3 (18.1)	57.7 (17.1)	0.812
Median (Q1, Q3)	65.0 (50.0, 70.0)	65.0 (48.5, 70.0)	62.5 (53.0, 69.2)	0.605
≤ 35 letters, *n* (%)	28.0 (14.6%)	15.0 (14.7%)	13.0 (14.4%)	1.000
≥ 70 letters, *n* (%)	60.0 (31.2%)	37.0 (36.3%)	23.0 (25.6%)	0.149

Q1 first quartile (25th percentile); *Q3* third quartile (75th percentile); *SD* standard deviation; *VA* visual acuity in logMAR letters

of women (41.4% vs. 66.9%, $p = 0.028$), an older mean age (85.3 vs. 81.1 years old, $p = 0.001$) but no differences in mean [SD] baseline VA (53.9 [21.1] vs. 58.8 [16.8], $p = 0.225$).

Discussion

This observational real-world study on nAMD treatment regimens has found TAE to deliver similar visual acuity results compared with a FB approach, with fewer injections in approximately a quarter of treated eyes, highlighting the possibility of overtreatment by fixed regimens approaches in a routine clinical setting. We report good visual acuity outcomes of TAE and FB regimens for nAMD with similar median number of injections, although the distribution of injections was wider in the TAE group with more eyes receiving fewer injections compared with FB.

The increasingly higher burden associated to nAMD treatment represents a significant public health challenge worldwide. IVT rates are expected to grow exponentially in the coming years [2, 22] due to population ageing and the chronic treatment–dependent maintenance of existing patients. There

Table 2 Visual outcomes at 12 months for treatment-naïve eyes comparing TAE vs. FB-treated eyes

	Treat-and-extend	Bimonthly	*p* value
Completers	86	74	
Baseline VA			
Mean (SD)	59.6 (17.1)	57.9 (16.5)	0.545
Median (Q1, Q3)	65.0 (50.0, 71.8)	60.0 (53.0, 69.2)	0.398
Final VA			
Mean (SD)	61.1 (20.0)	63.0 (16.5)	0.513
Median (Q1, Q3)	65.5 (50.0, 75.8)	68.5 (53.5, 75)	0.780
VA ≤ 35, % baseline/% final	14.0%/12.8%	13.5%/10.8%	0.936/0.700
VA ≥ 70, % baseline/% final	39.5%/41.9%	25.7%/50.0%	0.063/0.303
VA change			
Mean (95% CI)	1.5 (− 1.5, 4.5)	5.0 (1.3, 8.7)	0.148
Median (Q1, Q3)	2.0 (− 4, 8.8)	5.0 (0.0, 14.5)	0.068
Adjusted mean (95% CI)*	0.5 (− 2.1, 3.5)	5.2 (2.2, 8.3)	0.104
VA change, % loss/% gain			
≥ 5 letters	24.4%/38.4%	18.9%/55.4%	0.401/0.031
≥ 10 letters	14.0%/23.3%	13.5%/39.2%	0.936/0.029
≥ 15 letters	14.0%/15.1%	8.1%/25.7%	0.243/0.096
Active lesions, % visits	46.5%	55.6%	0.262
Injections, median (Q1, Q3)	7.0 (6.0, 8.0)	7.0 (7.0, 8.0)	0.410
Ranibizumab, %/Aflibercept, %	37.9%/62.1%	1.7%/98.3%	< 0.001

*Mean and median VA change adjusted for baseline VA and age

CI confidence interval; *Q1* first quartile (25th percentile); *Q3* third quartile (75th percentile); *SD* standard deviation; *VA* visual acuity in logMAR letters

Table 3 Visual outcomes at 24 months for treatment-naïve eyes comparing TAE vs. FB-treated eyes

	Treat-and-extend	Bimonthly	*p* value
Completers	46	33	
Baseline VA			
Mean (SD)	61.7 (15.1)	62.6 (14.6)	0.786
Median (Q1, Q3)	67.0 (50.0, 73.0)	65.0 (57.0, 75.0)	0.811
Final VA			
Mean (SD)	64.8 (15.4)	66.4 (16.2)	0.356
Median (Q1, Q3)	70.0 (57.5, 77)	75.0 (57.0, 77.0)	0.319
VA ≤ 35, % baseline/% final	8.7%/6.5%	6.1%/9.1%	0.663/0.671
VA ≥ 70, % baseline/% final	47.8%/56.5%	39.4%/57.6%	0.457/0.926
VA change			
Mean (95% CI)	3.1 (− 1.0, 7.1)	3.8 (− 1.9, 9.4)	0.408
Median (Q1, Q3)	2.5 (− 3.0, 11.5)	5.0 (0.0, 10)	0.315
Adjusted mean (95% CI)*	− 0.1 (− 3.2, 3.0)	3.6 (− 1.3, 8.6)	0.931
VA change, % loss/% gain			
≥ 5 letters	21.7%/39.1%	15.2%/60.6%	0.462/0.060
≥ 10 letters	15.2%/28.3%	9.1%/27.3%	0.419/0.923
≥ 15 letters	8.7%/21.7%	9.1%/18.2%	0.951/0.698
Active lesions, % visits	48.1%	47.3%	0.954
Injections, median (Q1, Q3)	11.0 (9.0, 13.0)	12.0 (11.0, 13.0)	0.742
Ranibizumab, %/Aflibercept, %	41.8%/58.2%	2.5%/97.5%	< 0.001

*Mean and median VA change adjusted for baseline VA and age

CI confidence interval; *Q1* first quartile (25th percentile); *Q3* third quartile (75th percentile); *SD* standard deviation; *VA* visual acuity in logMAR letters

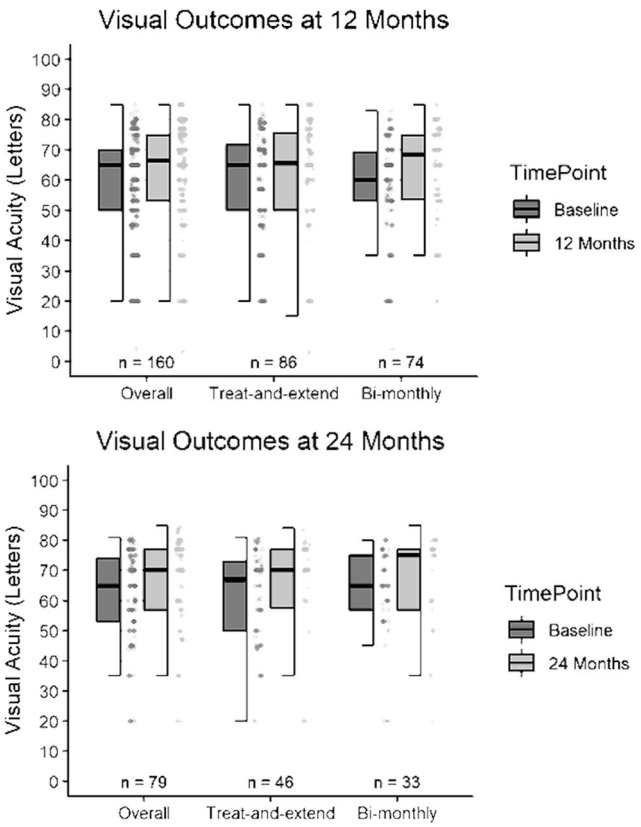

Fig. 1 Hybrid boxplot of visual outcomes at 12 months (above) and 24 months (below) for treatment-naïve 24-month completers (overall), treat-and-extend, and bi-monthly treated eyes. The whiskers represent the 25th and 75th quartiles plus or minus the interquartile range. Each dot represents an individual eye

is strong clinical evidence that supports the benefits of proactive treatment regimens, extending the effect of the injected drugs beyond the intended duration described in the original drug label. For instance, ranibizumab, which was originally licensed for a monthly-based regimen, had also been proven effective in TAE approaches in clinical trials [11]. Aflibercept, which was originally intended for bimonthly injections after a 3-monthly loading dose, had its drug label changed to allow a TAE approach after the loading dose according to clinical studies [23, 24].

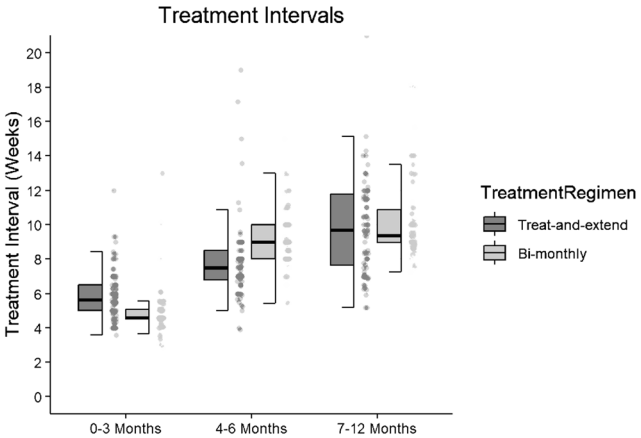

Fig. 2 Hybrid boxplot of treatment intervals at different time periods for treat-and-extend and bi-monthly treated eyes (12 months series). The whiskers represent the 25th and 75th quartiles plus or minus the interquartile range. Each dot represents an individual eye. Intervals: 4 weeks: 10–34 days; 6 weeks: 35–48 days; 8 weeks: 49–61 days; 10 weeks: 62–76 days; 12 weeks: 77–90 days; 14 weeks: 91–104 days; 16+ weeks: > 105 days

Table 4 Demographics partitioned by 12-month follow-up completers and noncompleters

	Completers	Noncompleters	*p* value
Eyes	160	32	
Patients	142	29	
Females, % patients	66.9%	41.4%	0.028
Age, mean (SD)	81.1 (7.4)	85.3 (6.3)	0.001
Baseline VA			
Mean (SD)	58.8 (16.8)	53.9 (21.1)	0.225
Median (Q1, Q3)	65.0 (50.0, 70.0)	62.5 (48.8, 66.2)	0.309
≤ 35 letters, *n* (%)	19 (11.9%)	6 (18.8%)	0.424
≥ 70 letters, *n* (%)	73 (45.6%)	7 (21.9%)	0.142

Q1 first quartile (25th percentile); *Q3* third quartile (75th percentile); *SD* standard deviation; *VA* visual acuity in logMAR letters

Considering nAMD as a common and chronic disease, one should however bear in mind that clinical trial outcomes may not always be translated to routine clinical care. Patient comorbidities, loss of follow-up and treatment of very good or very poor visual acuity cases—outside clinical trial visual acuity inclusion criteria—are issues in real-world nAMD practice that result in variation in visual improvements and other outcomes that are found less in clinical trials. These issues may represent a significant disadvantage of variable treatment intervals regimens compared to fixed regimens in routine clinical care [14, 20]. Several observational real-world data series have recently reported good visual acuity results of TAE approaches for nAMD [15, 25]. There is, however, a paucity of information about direct comparisons to compare the outcomes of TAE versus fixed regimens in a real-world setting.

The present study found similar VA outcomes of both TAE and FB regimens after 12 and 24 months of treatment. No statistically significant differences were found regarding VA change and final VA in either the 12 or 24-month cohorts (Tables 2 and 3, Fig. 1). Interestingly, both groups reached a final VA that was consistent with previously published reports in real life settings [16, 17, 20]. Although no statistically significant differences were observed, VA change in all analyses tended to favor FB, with a baseline- and age-adjusted mean at 12 months of + 0.5 TAE vs + 5.2 FB ($p = 0.104$) and at 24 months of − 0.1 TAE vs + 3.6 FB ($p = 0.931$). Furthermore, eyes within the FB group at 12 months had more eyes with ≥ 5 and ≥ 10 letter gains than the TAE group (Table 2) although these differences were not found at 24 months and proportions with VA loss were similar between the two groups. As a whole, even though no statistically significant differences were found in mean baseline VA for each group (Tables 2 and 3), a "floor effect" may still be found which may have conferred on the FB group a greater chance to obtain visual gains than the TAE group, as indeed was observed in our results [26]. Taking into account these considerations, we could conclude that no statistically significant differences in visual outcomes were observed between TAE and FB cases in our study cohort. Further research on larger cohorts may identify statistically significant differences where we have only observed trends.

In contrast, interestingly, we found important differences regarding the distribution of antiVEGF injection number, and therefore treatment intervals, between both treatment regimens (Tables 2 and 3, Fig. 2). This data is relevant, as it may highlight the potential of TAE to individualize treatment in each case and reduce the risk of under and overtreatment with fixed regimens in routine clinical care in selected eyes. As expected, injection numbers were less widely distributed in the FB treatment regimen cohort than in the TAE cohort. Whereas variation in treatment intervals when applying a FB regimen represents by definition a failure in the treatment plan, it may be expected in a real-life observation study, where not all patients can be managed under ideal conditions due to the limited capacity of the clinical units and the activity burden associated with routine clinical care. For instance, up to 25% of eyes in the FB cohort ended the first year of treatment receiving IVT 12-weekly. On the other hand, variability in the number of injections in the TAE group represent the core of this regimen's rationale, individualizing treatment according to the lesion activity in each specific case, keeping those patients with more active lesions on shorter treatment intervals and extending those with good response in longer ones. Of note, our finding that a notable proportion of active lesions, as defined by strict criteria that included the existence of subretinal fluid only on the OCT examination, still achieved good VA results is consistent with the findings of the FLUID randomized clinical trial that a degree of subretinal fluid may be tolerated without sacrificing visual gains [27].

Nonetheless, our TAE findings are consistent with those reported in both clinical trials and real world data studies [23, 25]. In summary, a TAE regimen allows the clinician to tailor and individualize the therapeutic approach to each patient. TAE has therefore allowed a quarter of the treated cases (Q1) to stay on longer treatment intervals In our series with fewer injections than the FB regimen (Tables 2 and 3) but with no differences in the median and third quartile (Q3) distribution of number of treatments, maintaining similar visual outcomes with both approaches.

This observational analysis has several strengths and limitations to disclose. One strength is that this sample of real world data provides important information on how treatment regimens perform in routine clinical practice outside the strict conditions of randomized clinical trial conditions, and as such its conclusions have high external validity [14, 20]. In addition, the FRB registry system is a well validated tool which assures the collection of high quality data and standardized measurements worldwide [21]. There are, however, some sources of potential bias. Since

patients were not randomly assigned to either group, selection bias may have occurred, even if no significant differences were observed in their participants' characteristics. In addition, as it is inherent to a real-life study, the lack of a strict treatment protocol may allow differences between physicians with regards to their grading of CNV lesion activity and therefore the reinjection frequency, a particularly important feature in the TAE group. Patients in the TAE group were treated with either predominantly ranibizumab or aflibercept so drug-related biases could also be present. However, recently published data on TAE approaches have found no differences between ranibizumab and aflibercept with regards to VA outcome and number of injections [23]. Finally, a degree of caution should be applied in interpreting the results of the present study since its observational nature resulted in a relatively high dropout rate after 24 months which may overestimate the benefits of treatment if patients discontinued treatment due to a poor result. In addition, 12-month noncompleters descriptive analysis, compared to the completers group, (Table 4) found no differences in baseline VA even though presenting with an older age and higher proportion of men, which could have influenced early dropout rate.

In conclusion, our study presents evidence that TAE reduces the burden of antiVEGF injections for nAMD in some eyes, maintaining similar visual outcomes in routine clinical care. Such information complements data from clinical trials and enhances current knowledge on how TAE performs in real world conditions, particularly in the number of injections needed to maintain good visual acuity outcomes. These results will be useful for future national and international multicenter studies of differences between dosing regimens and agents that seek to optimize the outcomes of antiVEGF therapies in individual nAMD patients in our clinics.

Data availability Data is available upon request to corresponding author.

Compliance with ethical standards

Conflict of interest MCG and DB are inventors of the software used to collect the data for this analysis. MFR reports personal fees from Allergan outside the submitted work. JZV reports personal fees from Allergan, Bayer, Novartis, and Roche outside the submitted work.

Ethics approval Institutional review board and ethics committee approvals were obtained from both study sites.

Consent to participate and for publication All study participants provided written informed consent.

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