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European Unmet Needs in the Management of Neovascular Age-Related Macular Degeneration in Daily Practice

Data from the Fight Retinal Blindness! Registry

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Purpose: To evaluate the proportion, predictors, and outcomes of patients with neovascular age-related macular degeneration (nAMD) treated with a high burden of VEGF inhibitor intravitreal (IVT) injections after 2 years in routine clinical practice.

Design: Retrospective analysis of data from a prospectively designed observational outcomes registry, the Fight Retinal Blindness! Project, of patients treated in European centers.

Participants: Treatment-naïve eyes (1 eye per patient) starting VEGF inhibitors for nAMD from January 2017 to March 2020 with 24 months of follow-up. We analyzed the following 3 treatment-burden groups defined by the mean interval of the 3 closest injections to the 24-month visit: (1) those with a high-treatment burden had injection intervals $\leq$ 42 days, (2) those with a low-treatment burden had injection intervals between 43 and 83 days; and (3) those with tolerable treatment burden had injection intervals between 84 and 365 days.

Methods: Multinomial regression was used to evaluate baseline risk predictors of patients requiring a high-treatment burden.

Main Outcome Measures: The proportion of patients that experienced a high-treatment burden at 2 years and its predictors.

Results: We identified 2038 eligible patients completing 2 years of treatment (2038/3943 patients [60%]) with a median (quartile 1, quartile 3) of 13 (10, 17) injections. The proportion of patients with a high-treatment burden was 25% (516 patients) at 2 years. Younger patients (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.96−0.99; $P < 0.01$) were more likely to have high-treatment burden, whereas eyes with type 3 choroidal neovascular lesions at baseline were significantly less likely (OR, 0.26; 95% CI, 0.13−0.52; $P < 0.01$). Regarding type of fluid, patients with subretinal fluid only at baseline (OR, 3.85; 95% CI, 1.34−11.01; $P = 0.01$) and persistent active intraretinal (OR, 1.56; 95% CI, 1.18−2.06; $P < 0.01$) or subretinal fluid only (OR, 2.21; 95% CI, 1.52−3.21; $P < 0.01$) after the loading phase had a higher risk of high treatment burden at 2 years.

Conclusions: High treatment burden is a common issue in routine clinical practice in Europe, with a quarter of patients requiring injections of conventional VEGF inhibitors every 6 weeks at 2 years and 40% discontinuing treatment within 2 years.

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Intravitreal (IVT) VEGF inhibitor therapy has transformed patient outcomes for neovascular age-related macular degeneration (nAMD) because it has been proven effective in registration trials.[1,2] Unfortunately, many patients with nAMD respond poorly to IVT treatment with VEGF inhibitors, which has become 1 of the most frequent procedures in many European countries.[3,4] Indeed, some patients require IVT with VEGF inhibitors every 4 to 8

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weeks to maintain their vision in the long term, representing a significant burden for our patients and the health care system.[5–9] Observational studies have highlighted that many patients are undertreated with a lower number of IVTs than expected in routine clinical practice.[10–12] The rates of nonadherence and nonpersistence in patients with nAMD treated with anti-VEGF are alarming.[13] The reasons for this in routine clinical practice are complex, but undertreatment can lead to irreversible visual loss.[14] The treatment burden of both visits and injections, as well as the waiting and travel time spent by patients and caregivers, play a key role in nonadherence in routine clinical practice.[14,15] Injection visit interval is a surrogate of treatment burden.

Novel long-acting drug agents or devices are under investigation, or have been recently approved for nAMD, with effectiveness that is noninferior to the conventional, approved VEGF inhibitor regimen with longer intervals between injections and a stronger drying effect on retinal fluid.[16–18] Their introduction in our practice gives hope to addressing the unmet need in managing our patients with nAMD who still require frequent injections. However, real-world data are still limited in the proportion and baseline predictors of those patients with nAMD considered as poor responders that could benefit most from longer-acting treatments in routine clinical practice. This study aimed to evaluate the proportion and baseline predictors of patients with nAMD with a high treatment burden using conventional VEGF inhibitors at 2 years in routine clinical practice using European data from the Fight Retinal Blindness (FRB!) Registry.

Methods

Study Design and Setting

Eligible patients were identified from the FRB! registry of observational outcomes. The FRB! registry tracks outcomes of patients with nAMD in routine clinical practice and is compliant with the International Consortium of Healthcare Outcome Measurement's minimum standard set of treatment outcomes for macular degeneration.[19]

Patients from Austria, Belgium, France, Ireland, Italy, Netherlands, Portugal, Slovakia, Spain, Lebanon, and Switzerland were included. All centers obtained approvals from their own relevant local ethics and data protection committees. The data were deidentified at the time of submission before analysis. All patients gave their informed consent. Informed consent ("opt-in consent") was obtained for each country in compliance with the European General Data Protection Regulations. This study adhered to the tenets of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology statements for reporting observational studies.[20]

Data Sources/Measurements

Data were recorded from each clinical visit by the treating physician and included visual acuity (VA) measured by the number of letters read on a logarithm of the minimum angle of resolution chart (best of corrected, uncorrected, or pinhole); treatment given (if any); activity of the choroidal neovascular (CNV) lesion graded as "inactive," "active" (any combination of intraretinal fluid [IRF], subretinal fluid [SRF], or hemorrhage excluding SRF only), hereafter referred to as "active IRF", or "active (SRF only)"; and adverse events. Macular atrophy and subretinal fibrosis were graded at each visit as either subfoveal, extrafoveal, or not present based on clinical examination, OCT, or dye angiography, alone or in combination. Previous treatments and angiographic lesion subtype were recorded at the baseline visit. All treatment decisions, including the retreatment schedule, were determined by the treating physician in consultation with the patient with no intervention by the investigators.

Study Population and Groups

We identified treatment-naïve eyes with nAMD from European countries in the FRB! registry initiating treatment with VEGF inhibitor IVT from January 1, 2017 (the activity of the CNV lesion was previously graded only as either "active" or "inactive" for data entered before January 2017), until March 30, 2020, to allow for up to 2 years of follow-up. Eyes were also required to have received a minimum of 3 injections with no gaps between visits exceeding 365 days to establish ongoing treatment. The present study only included patients whose entire visit history includes the new CNV gradings. When both eyes were being treated in a single patient, we included only the eye that received treatment first.

Patients were grouped according to their treatment burden at 24 months, defined by the mean treatment interval for the 3 injections closest to and including the 24-month visit. The treatment-burden groups were defined as follows:

1. Tolerable treatment burden: mean treatment interval between 84 days and 365 days
2. Low treatment burden: mean treatment interval between $>$ 42 days and $<$ 84 days
3. High treatment burden: mean treatment interval $\leq$ 42 days. This group was further divided into those whose CNV lesion was "recently active" (i.e., CNV graded as "active" at $\geq$ 1 of their last 3 visits) or "recently inactive" (i.e., CNV graded as "inactive" at the last 3 visits).

Outcome Measures

The primary outcome was the proportion of eyes in the high-treatment-burden group at 24 months. Secondary outcomes included visual and treatment outcomes over 24 months, baseline predictors of high treatment burden and ocular adverse events.

Statistical Analysis

Descriptive statistics included mean, standard deviation (SD), median, first quartile (Q1) and third quartile (Q3), and percentages, as appropriate. Visual acuity over 24 months between treatment burden groups was visualized using generalized additive models.

Predictive factors for treatment burden group were analyzed using multinomial regression with baseline gender, age, VA, CNV lesion type, presence of macular atrophy or subretinal fibrosis, and CNV lesion activity, as well as the 3-month change in VA and CNV activity after loading, with the tolerable treatment burden group as the reference group. Univariate models for each predictor were followed by a multivariate model, including all the predictors.

A P value of $<$ 0.05 was considered statistically significant. All analyses were conducted using R Statistical Software (version 4.2.1) with the mgcv package (version 1.8-40) for generalized

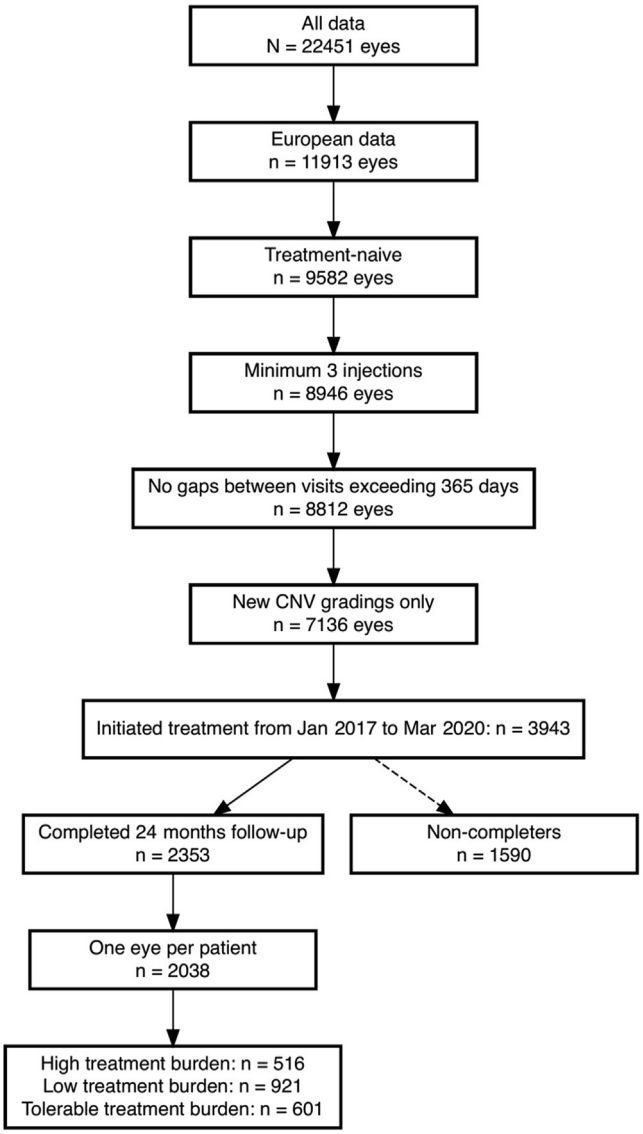

Figure 1. Flowchart showing the number of eyes at each selection criteria. CNV = choroidal neovascular.

additive models and the nnet package (version 7.3-17) for multinomial models.

Results

Study Population

A total of 2038 patients were identified as eligible for our analysis. The number of patients at each selection criterion is shown in Figure 1. The baseline clinical and demographic characteristics are described in Table 1. Most patients were women (60%) and the mean (SD) age was 78.8 (8.2) years. The mean (SD) baseline VA was 58.5 (20.5) letters. Regarding the type of CNV lesion, 27%, 11%, and 6% of patients had type 1, type 2, and type 3 CNV, respectively. Most patients did not have macular atrophy (84%) or subretinal fibrosis (87%) at the start of the treatment. Most eyes had active IRF (80%) at presentation, whereas 18% had SRF only (Table 1).

Treatment Burden Outcomes at 2 Years

The proportion of patients with a high treatment burden at 24 months was 25% (516 patients), with a median (Q1, Q3) injection interval of the last 3 injections of 32.7 (29.0, 37.3) days (Table 2). Of those patients, 59% and 41% had their CNV activity graded as "recently active" and "recently inactive" at the last visits before 2 years, with a median (Q1, Q3) injection interval of 32.7 (28.7, 37.3) days and 33.3 (29.5, 37.9) days, respectively. The proportions of patients with a low and tolerable treatment burden at 2 years were 45% (921 patients) and 30% (601 patients), respectively.

After the loading phase at 3 months, approximately 40% (845 patients) of the overall cohort had inactive CNV lesion. The proportion of inactive CNV lesion at 3 months was greater in patients with tolerable treatment burden (48%) at 2 years compared with patients with low treatment burden (41%) and high treatment burden (34%). Overall, 41% (845 patients) of the patients had CNV activity graded as inactive at 24 months, whereas 59% (1193 patients) had active CNV with IRF in 41% (845 patients) and SRF only in 18% (358 patients; Table 2). Among patients with high treatment burden at 2 years, 41% (214 patients) were defined as "recently inactive, whereas 59% (302 patients) were considered as "recently active." Many patients with low and tolerable treatment burden still had CNV activity graded as recently active at 2 years: 58% (539 patients) and 52% (311 patients), respectively (Table 2).

Baseline risk predictors of high and low treatment burden using a multinomial regression model are shown in Table 3. Younger patients (odds ratio [OR], 0.97 each incremental year; 95% confidence interval (CI), 0.96−0.99; $P < 0.01$) and patients with isolated SRF (OR, 3.85; 95% CI, 1.34−11.01; $P = 0.01$) at baseline were significantly more likely to have a high treatment burden at 2 years. Patients with type 3 CNV at baseline were less likely to have a high treatment burden at 2 years (OR, 0.26; 95% CI, 0.13−0.52; $P < 0.01$; Table 3). After the loading phase of 3 injections, eyes that had active CNV with IRF (OR, 1.56; 95% CI, 1.18−2.06; $P < 0.01$) or SRF only (OR, 2.21; 95% CI, 1.52−3.21; $P < 0.01$) were at higher risk of high treatment burden at 2 years, whereas the mean 3-month VA change from baseline did not predict the risk of subsequent high treatment burden. Baseline VA and the presence of geographic atrophy (GA) or subretinal fibrosis were not significantly associated with the treatment burden at 2 years (Table 3).

Visual and Treatment Outcomes at 24 Months

Visual and treatment outcomes over 24 months are reported in Table 2 and Figure 2. Overall, the mean (95% CI) change in VA from baseline in all eyes was 3.1 (2.3−3.9) letters at 24 months. There was no significant difference in the visual outcome between groups after the loading phase at 3 months and 24 months, with a mean VA change at 24 months of +4.0 (2.4−5.6) letters in the high, +3.6 (2.4−4.8) letters in the low, and +1.5 (−0.1 to 3.1) letters in the tolerable-treatment-burden groups (Table 2, Fig 2). Thirty-three percent, 31%, and 29% of patients achieved a 1-line VA gain; whereas 12%, 10%, and 9% lost the same amount at 24 months in the high-, low-, and tolerable-treatment-burden groups, respectively (Table 2).

Table 1. Demographics for all Eyes Completing 24 Months of Treatment Follow-up, and Stratified by Whether Their Treatment Burden at 24 Months Was High, Low, or Tolerable

		High Treatment Burden				
	Overall Cohort	*Recently Active*	*Recently Inactive*	*Overall*	Low Treatment Burden	Tolerable Treatment Burden
Eyes, n (%)	2038 (100%)	302 (15%)	214 (11%)	516 (25%)	921 (45%)	601 (29%)
Patients, n (%)	2038 (100%)	302 (15%)	214 (11%)	516 (25%)	921 (45%)	601 (29%)
Gender (female), n (%)	1226 (60%)	168 (56%)	135 (63%)	303 (59%)	550 (60%)	373 (62%)
Smoking status, n (%)						
Smoker	85 (4%)	19 (6%)	8 (4%)	27 (5%)	33 (4%)	25 (4%)
Nonsmoker	509 (25%)	76 (25%)	59 (28%)	135 (26%)	223 (24%)	151 (25%)
Ex-smoker	240 (12%)	61 (20%)	32 (15%)	93 (18%)	105 (11%)	42 (7%)
Unknown	1204 (59%)	146 (48%)	115 (54%)	261 (51%)	560 (61%)	383 (64%)
Baseline age (yrs), mean (SD)	78.8 (8.2)	76.8 (9)	79.1 (8.2)	77.8 (8.7)	78.7 (8.1)	79.7 (7.8)
Baseline VA (letters), mean (SD)	58.5 (20.4)	60.8 (18.7)	56.3 (23.5)	58.9 (20.9)	58.8 (19.5)	57.6 (21.3)
≤ 35 letters, n (%)	303 (15%)	29 (10%)	40 (19%)	69 (13%)	128 (14%)	106 (18%)
36–69 letters, n (%)	976 (48%)	153 (51%)	94 (44%)	247 (48%)	460 (50%)	269 (45%)
≥ 70 letters, n (%)	759 (37%)	120 (40%)	80 (37%)	200 (39%)	333 (36%)	226 (38%)
CNV lesion type, %						
Type 1	549 (27%)	104 (34%)	56 (26%)	160 (31%)	242 (26%)	147 (24%)
Type 2	230 (11%)	37 (12%)	21 (10%)	58 (11%)	96 (10%)	76 (13%)
Type 3	115 (6%)	0 (0%)	12 (6%)	12 (2%)	53 (6%)	50 (8%)
Other	72 (4%)	9 (3%)	8 (4%)	17 (3%)	30 (3%)	25 (4%)
Not recorded	1072 (53%)	152 (50%)	117 (55%)	269 (52%)	500 (54%)	303 (50%)
Macular atrophy, n (%)						
Subfoveal	204 (10%)	23 (8%)	28 (13%)	51 (10%)	94 (10%)	59 (10%)
Extrafoveal	125 (6%)	9 (3%)	17 (8%)	26 (5%)	52 (6%)	47 (8%)
Not present	1709 (84%)	270 (89%)	169 (79%)	439 (85%)	775 (84%)	495 (82%)
Subretinal fibrosis, n (%)						
Subfoveal	231 (11%)	28 (9%)	29 (14%)	57 (11%)	111 (12%)	63 (10%)
Extrafoveal	32 (2%)	2 (1%)	5 (2%)	7 (1%)	17 (2%)	8 (1%)
Not present	1775 (87%)	272 (90%)	180 (84%)	452 (88%)	793 (86%)	530 (88%)
CNV activity, n (%)						
Active IRF	1626 (80%)	234 (77%)	166 (78%)	400 (78%)	726 (79%)	500 (83%)
Active SRF only	375 (18%)	66 (22%)	45 (21%)	111 (22%)	179 (19%)	85 (14%)
Inactive	37 (2%)	2 (1%)	3 (1%)	5 (1%)	16 (2%)	16 (3%)

CNV = choroidal neovascular; IRF = intraretinal fluid; SD = standard deviation; SRF = subretinal fluid; VA = visual acuity.

Overall, the median (Q1, Q3) number of injections was 13 (10, 17) at 2 years. The median number of injections over 2 years increased according to treatment burden groups, with 10 (8, 12) in the tolerable-treatment-burden group, 14 (11, 16) in the low-treatment-burden group, and 19 (14, 23) injections in the high-treatment-burden group (21 [17, 24] for "recently active" subgroup vs. 16 [4, 21] for "recently inactive" subgroup). The median number of visits over 2 years followed the same trend as the number of injections in each group (Table 2).

Noncompletion

Forty-eight percent of eyes that had first treatment between January 2017 and March 2020 were excluded from the study due to non-completion of 24 months (1590/3943 [40%]) or because they were the second eye being treated (315/3943 [8%]). Noncompletion occurred at a median (Q1, Q3) of 350 days (185, 506). Reasons for discontinuation were recorded in 330/1590 noncompleters (21%), including "Treatment futility" (173/330 eyes [52%]), "Patient declined" (35/330 eyes [11%]), "Treatment successful" (37/330 eyes [11%]), "Going to another doctor" (36/330 eyes [11%]), "Medical contraindication" (6/330 eyes [2%]), or "Deceased" (43/330 eyes [13%]). Baseline demographics and outcomes at final review are described in Tables S4 and S5 (available at www.ophthalmologyretina.org). Overall, noncompleters tended to have a lower mean starting VA (55 vs. 62 letters) and mean visual change (+1 vs. +3 letters) at 24 months than completers.

Safety

A summary of ocular adverse events is shown in Table 6. We did not find significant discrepancies in the rate of reported ocular adverse events over 2 years between treatment burden groups, notably in the rate of endophthalmitis.

Discussion

This study aimed to evaluate the nAMD treatment burden in a European population 2 years after the start of VEGF inhibitor IVT therapy using the FRB! outcomes registry. We found that intensive therapy with repeated IVT injections, every 6 weeks or less, in treated patients with nAMD is common in Europe in daily practice. The proportions of patients with nAMD with high (i.e., injections every ≤ 6 weeks), low (i.e., injections every > 6 to < 12 weeks), and tolerable (i.e., injections every ≥ 12 weeks) treatment

Table 2. Outcomes at 24 Months Stratified by Whether Their Treatment Burden at 24 Months Was High, Low, or Tolerable

	Overall Cohort	High Treatment Burden			Low Treatment Burden	Tolerable Treatment Burden
		Recently Active	*Recently Inactive*	*Overall*		
Eyes, n (%)	2038	302 (15%)	214 (10%)	516 (25%)	921 (45%)	601 (30%)
Response to loading						
3-mo VA change from baseline, mean (95% CI)	4.2 (3.7–4.7)	4.3 (2.8–5.7)	4.2 (2.5–6)	4.3 (3.2–5.4)	4.2 (3.4–4.9)	4.2 (3.2–5.2)
3-mo CNV active IRF, n (%)	835 (41%)	149 (49%)	69 (32%)	218 (42%)	380 (41%)	237 (39%)
3-mo CNV active SRF only, n (%)	358 (18%)	81 (27%)	44 (21%)	125 (24%)	159 (17%)	74 (12%)
3-mo CNV inactive, n (%)	845 (41%)	72 (24%)	101 (47%)	173 (34%)	382 (41%)	290 (48%)
24-mo visual outcomes						
VA, mean (SD)	61.5 (21.5)	65.2 (18.4)	60.1 (25.2)	63.1 (21.6)	62.2 (20.3)	59.0 (22.9)
VA change from baseline, mean (95% CI)	3.1 (2.3–3.9)	4.1 (2.1–6.1)	3.9 (1.2–6.5)	4.0 (2.4–5.6)	3.6 (2.4–4.8)	1.5 (−0.1 to 3.1)
Gain > 5 letters, n (%)	625 (31%)	106 (35%)	65 (30%)	171 (33%)	281 (31%)	173 (29%)
Gain 1–5 letters, n (%)	349 (17%)	58 (19%)	37 (17%)	95 (18%)	160 (17%)	94 (16%)
Loss 0–5 letters, n (%)	863 (42%)	97 (32%)	93 (43%)	190 (37%)	391 (42%)	282 (47%)
Loss > 5 letters, n (%)	201 (10%)	41 (14%)	19 (9%)	60 (12%)	89 (10%)	52 (9%)
Loss > 10 letters, n (%)	99 (5%)	22 (7%)	13 (6%)	35 (7%)	42 (5%)	22 (4%)
Loss > 15 letters, n (%)	55 (3%)	13 (4%)	8 (4%)	21 (4%)	24 (3%)	10 (2%)
24-mo CNV activity, n (%)						
Active IRF	835 (41%)	149 (49%)	69 (32%)	218 (42%)	380 (41%)	237 (40%)
Active SRF only	358 (18%)	81 (27%)	44 (21%)	125 (24%)	159 (17%)	74 (12%)
Inactive	845 (41%)	72 (24%)	101 (47%)	173 (34%)	382 (42%)	290 (48%)
24-mo injection frequency						
Injection interval last 3 injections, median (Q1, Q3)	64 (42, 90.3)	32.7 (28.7, 37.3)	33 (29.5, 37.3)	32.7 (29, 37.3)	63 (53.7, 71)	107.3 (93.3, 135.7)
Total injections, median (Q1, Q3)	13 (10, 17)	21 (17, 24)	16 (4, 20.8)	19 (14, 23)	14 (11, 16)	10 (8, 12)
Total visits, median (Q1, Q3)	18 (14, 22)	24 (21, 27)	19 (13, 24)	23 (18, 26)	18 (15, 21)	14 (12, 17)

CI = confidence interval; CNV = choroidal neovascular; IRF = intraretinal fluid; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SRF = subretinal fluid; VA = visual acuity.

burden at 2 years were 25%, 45%, and 30%, respectively. Unsurprisingly, high-treatment-burden patients had a significantly greater median (Q1, Q3) number of injections (19 [14, 23]) and visits (23 [18, 26]) at 2 years than low-treatment-burden patients (14 [11, 16] injections and 18 [15, 21] visits) and tolerable-treatment-burden patients (10 [8, 12] injections and 14 [12, 17] visits), which emphasizes that the injection visit interval is a good biomarker of treatment burden.

Of those with a high treatment burden, approximately 60% had recently active CNV lesions at 2 years, showing that a significant number of patients with nAMD were poorly responsive to approved VEGF inhibitors and remained at intensive injection frequency due to persistent signs of exudation, which are associated with inferior visual outcomes. Mechanisms contributing to suboptimal response are still not understood and likely to be multifactorial, including recalcitrant genetic profile, environmental factors (smoking), drug tachyphylaxis, higher levels of VEGF, or production of non–VEGF-related neovascularization pathway cytokine.[5] Numerous definitions of poor response to VEGF inhibitors in nAMD have been published in the literature, with varying criteria and names, such as refractory, resistant, or recalcitrant nAMD. Our analysis showed that a persistent active CNV lesion with intraretinal (OR, 1.56; 95% CI, 1.18–2.06; $P < 0.01$) or subretinal fluid only (OR, 2.21; 95% CI, 1.52–3.21; $P < 0.01$) after the loading phase were at a higher risk of high treatment burden at 2 years. Consistently, most authors have agreed that eyes with persistent exudative signs on multimodal imaging after 3 to 6 months of monthly anti-VEGF injections are subsequently responding suboptimally.[5,6] The Comparison of AMD Treatments Trial study reported a significant proportion of persistent activity at 2 years with 86% and 54.5% of patients with fluid in the bevacizumab-as-needed group and the monthly ranibizumab group, respectively.[2]

On the other hand, we found that approximately half of the patients with low and tolerable treatment burden still had signs of CNV activity at 2 years, although they had received fewer injections. The FRB! registry database infers, rather than specifically collects, data on the treatment regimen. However, injections of eyes at > 80% of visits in the overall cohort reflect a treat-and-extend (TAE) regimen,[12] which has been widely used in the retina physician community for over a decade. A recent literature review reported patients' preference for the TAE regimen over a fixed regimen because of the perceived reduction in treatment burden.[21] During a TAE regimen, the interval of injections after a loading dose is progressively extended or reduced by 1 to 2 weeks according to the presence of signs of disease recurrence, such as changes in VA or signs of retinal fluid.[7,9] Treating physicians may have tolerated signs of exudation in some patients who refused a high treatment burden. A previous study of the FRB! on the TAE regimen found that 34% and 15% of treated eyes had

Table 3. Baseline Risk Predictors of the High- and Low-Treatment-Burden Group vs. Tolerable Using Multinomial Regression

	High Treatment Burden				Low Treatment Burden			
	Odds Ratio (95% CI; Reference = Tolerable)				Odds Ratio (95% CI; Reference = Tolerable)			
Variable (reference)	Univariate	P Value	Multivariate	P Value	Univariate	P Value	Multivariate	P Value
Baseline predictors								
Gender (female)								
Male	1.17 (0.92–1.49)	0.19	1.12 (0.87–1.43)	0.38	1.12 (0.91–1.39)	0.28	1.08 (0.88–1.34)	0.46
Baseline age, per yr	0.97 (0.96–0.98)	< 0.01*	0.97 (0.96–0.99)	< 0.01*	0.98 (0.97–1.00)	0.01*	0.98 (0.97–1.00)	0.02*
Baseline VA, per letter	1.00 (1.00–1.01)	0.19	1.00 (1.00–1.01)	0.58	1.00 (1.00–1.01)	0.27	1.00 (1.00–1.01)	0.42
CNV lesion type (type 1)								
Type 2	0.70 (0.47–1.05)	0.09	0.75 (0.49–1.13)	0.17	0.76 (0.53–1.10)	0.14	0.79 (0.55–1.15)	0.22
Type 3	0.22 (0.11–0.43)	< 0.01*	0.26 (0.13–0.52)	< 0.01*	0.64 (0.41–0.99)	0.04*	0.73 (0.47–1.14)	0.17
Other	0.62 (0.32–1.20)	0.16	0.60 (0.31–1.17)	0.13	0.72 (0.41–1.28)	0.26	0.71 (0.40–1.26)	0.24
Not recorded	0.81 (0.61–1.07)	0.14	0.87 (0.66–1.16)	0.34	0.99 (0.77–1.28)	0.96	1.04 (0.81–1.35)	0.74
Geographic atrophy (not present)								
Subfoveal	0.92 (0.61–1.36)	0.66	0.95 (0.62–1.44)	0.81	0.98 (0.70–1.38)	0.91	0.96 (0.67–1.37)	0.80
Extrafoveal	0.59 (0.36–0.97)	0.04*	0.66 (0.40–1.09)	0.10	0.67 (0.45–1.01)	0.05	0.69 (0.46–1.04)	0.08
Subretinal fibrosis (not present)								
Subfoveal	1.02 (0.70–1.50)	0.90	1.09 (0.72–1.64)	0.69	1.17 (0.85–1.63)	0.34	1.26 (0.88–1.79)	0.21
Extrafoveal	1.03 (0.37–2.85)	0.96	1.12 (0.39–3.19)	0.84	1.42 (0.61–3.31)	0.42	1.60 (0.67–3.81)	0.29
CNV activity (inactive)								
Active IRF	2.54 (0.92–6.98)	0.07	2.58 (0.93–7.18)	0.07	1.55 (0.76–3.16)	0.23	1.68 (0.81–3.46)	0.16
Active SRF only	4.27 (1.50–12.11)	0.01*	3.85 (1.34–11.01)	0.01*	2.29 (1.08–4.84)	0.03*	2.29 (1.07–4.89)	0.03*
3-mo predictors								
VA change, per letter	1 (0.99–1.01)	0.93	1 (0.99–1.02)	0.4	1 (0.99–1.01)	0.95	1 (0.99–1.01)	0.43
CNV activity (inactive)								
Active IRF	2.56 (0.93–7.05)	0.07	1.56 (1.18–2.06)	< 0.01*	1.45 (0.72–2.93)	0.30	1.28 (1.01–1.62)	0.04*
Active SRF only	4.18 (1.47–11.86)	0.01*	2.21 (1.52–3.21)	< 0.01*	2.11 (1.01–4.41)	0.05	1.35 (0.96–1.89)	0.09

CI = confidence interval; CNV = choroidal neovascular; IRF = intraretinal fluid; SRF = subretinal fluid; VA = visual acuity. *Statistically significant *P* values.

unchanged and increased injection intervals after the first CNV reactivation, respectively.[8] The American Society of Retina Specialists global trends survey in 2021 reported that 57.1% of European retina specialists would tolerate recurrent extrafoveal SRF on a TAE protocol. Another explanation could be that CNV activity could be recorded as falsely "active." Outer retinal tubulations or nonexudative intraretinal cysts could be a sign of nonexudative AMD that could be taken inadvertently as signs of CNV lesion activity.[22]

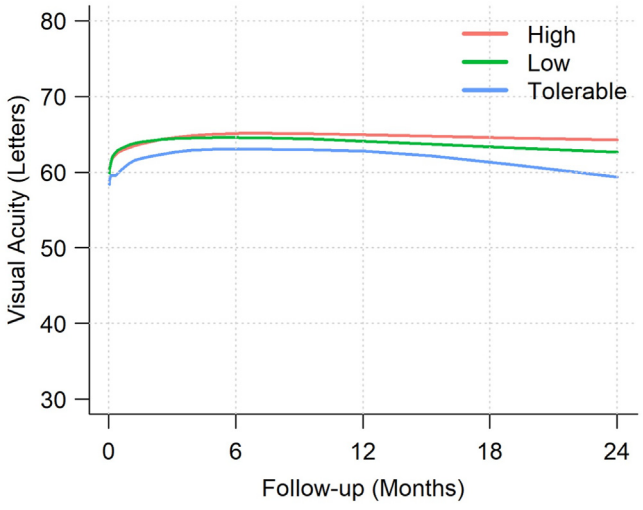

Figure 2. Line graph of the predicted visual acuity according to the treatment burden groups from baseline to 24 months.

Real-world studies have reported undertreatment of nAMD, with patients receiving fewer intravitreal injections than recommended by the different treatment schema.[10–12,23,24] The median (SD) number of total injections was 13 (10, 17) over 2 years in our study, which is relatively high compared with other observational studies.[10–12,23–25] Our results are more consistent with the recommended number of injections found using strict regimen protocol in randomized controlled trials.[1,2] Mean VA change (95% CI) in our study was 3.1 ETDRS letters (2.3–3.9), which is higher than some observational studies, probably due to the high number of injections.[24] Our cohort also had mostly type 1 CNV lesions, which has been reported to have a more favorable outcome if undertreated than type 2 CNV lesions, possibly because they are less likely to cause subretinal fibrosis and structural damage of the retina.[2,6]

Few observational studies have reported the effect of mean injection intervals with treatment outcomes. Previous FRB! analyses, with smaller sample sizes, have reported a higher proportion of nAMD eyes with a high treatment burden at 2 years, which ranged from 45% to 55%.[7,9] The Treatment Outcome of Wet Age-Related Macular Degeneration Management in Thailand study, a

Table 6. Summary of Adverse Events and Rates per Injection Recorded during the Study Period

	Adverse Events, n (Rate per Injection) Over 24 mos		
	High Treatment Burden	*Low Treatment Burden*	*Tolerable Treatment Burden*
Anterior uveitis	0 (0%)	1 (0.007%)	0 (0%)
Hemorrhage with loss of ≥ 15 letters	7 (0.068%)	10 (0.068%)	1 (0.015%)
Infectious endophthalmitis	1 (0.01%)	3 (0.02%)	2 (0.03%)
Noninfectious endophthalmitis	5 (0.049%)	2 (0.014%)	1 (0.015%)
Retinal detachment	2 (0.02%)	2 (0.014%)	0 (0%)
Retinal pigment epithelial tear	11 (0.108%)	21 (0.142%)	3 (0.045%)
Total injections	10 224	14 754	6712

retrospective real-world study, found an average interval of < 8 weeks (56 days) in 50% of the patients after a 2-years follow-up.[26] Still, the mean number of injections was lower, with < 10 injections. Our study reported that 29% of patients had tolerable treatment burden at 2 years, which seemed consistent with other reports that range from 21% to 32%. Less influenced by the rate of dropout, recently published prospective studies reported that approximately 40% of eyes had an interval of > 12 weeks at 2 years.[27,28]

A multivariate multinomial model found that younger patients (OR, 0.97 each incremental year; 95% CI, 0.96−0.97; $P < 0.01$) were significantly more at risk of a high treatment burden at 2 years, whereas patients with type 3 CNV lesion at baseline were less at risk (OR, 0.26; 95% CI, 0.13−0.52; $P < 0.01$). Regarding type of fluid, patients with SRF only at baseline (OR, 3.85; 95% CI, 1.34−11.01; $P = 0.01$) or persistent active intraretinal (OR, 1.56; 95% CI, 1.18−2.06; $P < 0.01$) or SRF only (OR, 2.21; 95% CI, 1.52−3.21; $P < 0.01$) after the loading phase had a higher risk of high treatment burden at 2 years. Older age has already been reported to be a predictor of poor response in nAMD.[5] Treating physicians may have treated younger patients more aggressively because they might be more compliant and adherent to a high treatment burden.[13] Younger patients usually have a better visual prognosis than older patients, which might have incited physicians to treat them aggressively to maintain vision over the long term. Type 3 CNV lesion has been shown to have an excellent response to anti-VEGF.[29,30] A previous FRB! study reported better mean VA change at 24 months than matched controls with other CNV lesion types.[29] Both groups received 13 injections over 2 years despite lower activity in the type 3 CNV group, suggesting that we tend to overtreat type 3 CNV, which may confer higher risk of GA leading to vision loss in this subtype of CNV. We found that recently published works may have changed physicians' treatment practice, with fewer patients with type 3 CNV in the high-treatment-burden group at 2 years.[29,30] However, this finding should be taken with caution because only 6% of patients were recorded with type 3 CNV lesion. Subretinal fluid at baseline and persistent intraretinal or subretinal fluid after the loading phase seem to be good predictors of high treatment burden at 2 years in our multivariate analysis, whereas baseline vision and functional response at 3 months were not predictive of subsequent high treatment burden at 2 years. The literature has reported discrepancies between the presence of SRF and the number of injections required over time.[31] Authors in favor of tolerating SRF have suggested that it could help decrease the treatment burden and the risk of macular atrophy secondary to VEGF inhibitors.[32] The FLUID study tested the hypothesis that tolerating some SRF in patients with nAMD with TAE regimen could achieve similar results with fewer injections than completely resolving SRF.[32] They reported noninferiority of tolerating SRF in visual outcomes than intensively treating SRF at 2 years. More eyes achieved 12-week intervals in the relaxed group than in the intensive group (29.6% vs. 15.0%, $P = 0.005$), leading to fewer injections with similar final VA. Our analysis showed that physicians did not seem to tolerate SRF when treating patients with nAMD in routine clinical practice.

The rates of adverse events related to intravitreal therapy in our real-world study are consistent with the literature and did not seem to increase with a higher frequency of injections, notably for endophthalmitis.[7−9] Our results align with a previous study from Daien et al,[33] which reported a similar rate of endophthalmitis with each injection, and no increased risk with successive injections.

Forty percent of patients did not complete the 2-year visit and were excluded from our analysis. Nonpersistence and nonadherence to treatment in nAMD remain significant issues in routine clinical practice.[14] Real-world studies on the treatment outcomes of VEGF inhibitors in nAMD have reported similar dropout rates of around 25% at 1 year and 35% at 2 years.[7,11] The relatively high proportion of noncompleters might have underestimated the actual European nAMD treatment burden in routine clinical practice. Furthermore, excluded noncompleters tended to have lower presenting vision and visual gain than included completers in our analysis. Collected reasons for discontinuation were likely to be related to poor outcomes in most cases (52% of patients considered "treatment to be futile"). These findings emphasize that poor short-term visual outcomes in nAMD cause treatment discontinuation in daily practice.

The limitations of the study are those inherent to observational studies.[34] The selection of cases and treatment regimens might vary among clinicians, and treatment decisions are made without adjudication from a reading center or a specific study protocol. Dosing frequency can vary according to the patient's ocular or general situation and may not mirror the intended dosing frequency,

reflecting routine clinical practice. However, real-world studies provide data on the ability of a treatment to achieve its intended purpose in daily practice and are more generalizable. Our data represent a wide variety of European practices and practitioners with a significant number of completers at 2 years. Although there is variability in the data quality in observational studies, the FRB! system includes quality assurance measures that preclude out-of-range and missing data.[35,36] Finally, differences in outcomes between drugs were not studied in our analysis because it would have been difficult to infer any conclusion on efficacy between drugs from our data. Clinical trials and real-world studies have shown that ranibizumab and aflibercept have similar short- and long-term outcomes for treating nAMD.[35]

In conclusion, unmet needs remained a common issue in the management of nAMD in European daily practice after 2 years of conventional VEGF inhibitor injections, with a quarter of patients still treated every 6 weeks or less and 40% discontinuing treatment by 2 years. Longer-acting therapeutics might alleviate treatment constraints in the management of nAMD.[16–18]

Footnotes and Disclosures

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Abbreviations and Acronyms:
CI = confidence interval; **CNV** = choroidal neovascular; **FRB!** = Fight Retinal Blindness; **GA** = geographic atrophy; **IRF** = intraretinal fluid; **IVT** = intravitreal; **nAMD** = neovascular age-related macular degeneration; **OR** = odds ratio; **Q1** = first quartile; **Q3** = third quartile; **SD** = standard deviation; **SRF** = subretinal fluid; **TAE** = treat-and-extend; **VA** = visual acuity.

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