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Creation of a neovascular age-related macular degeneration national database using a web-based platform: Fight Retinal Blindness Spain. Report 1: Visual outcomes

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Abstract

Background: To study the visual outcomes of neovascular AMD (nAMD) treated with anti-vascular endothelial growth factor (VEGF) drugs at national level.

Methods: Multicenter national database of nAMD eyes treated with anti-VEGF intravitreal injections (ranibizumab, aflibercept, bevacizumab) in fixed bimonthly (FB) or treat-and-extend (TAE) regimens. Demographics, visual acuity (VA) in logarithm of the minimum angle of resolution (logMAR) ETDRS letters at baseline and subsequent visits, number of injections and visits data were collected using a validated web-based tool (Fight Retinal Blindness!).

Results: 1273 eyes (1014 patients) were included, 971 treatment naïve (TN) and 302 previously treated (PT). Baseline VA (mean ± SD) was 57.5 (±19.5) and 62.2 (±17) ($p > 0.001$), and 24 months final VA was 60.4 (±21.2) and 58.8 (±21.1) ($p = 0.326$), respectively. Mean VA change at 12/24 months was +4.2/+2.9 letters in TN eyes and +0.1/−3.4 letters in PT eyes ($p < 0.001/p < 0.001$). The percentage of ≥15 letters gainers/losers at 24 months was 24.8%/14.5% in TN, and 10.3%/15.7% in PT eyes. The median number of injections/visits at 12 months was 7/9 in TN and 6/8 in PT ($p = 0.002/p < 0.001$) and at 24 months was 11/16 in TN and 11/14 in PT ($p = 0.329/p < 0.001$). Study drugs included ranibizumab (39.5%), aflibercept (41.2%) and bevacizumab (19.3%).

Javier Zarranz-Ventura and Alba Parrado-Carrillo have contributed equally to the manuscript and should be considered equivalent first authors.

A complete list of members of the FRB! Spain Users Group is detailed in Appendix S1.

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Conclusion: Independent, large-scale national audits are feasible if committed health care professionals are provided with efficient information technology systems to do them. The results described here represent an adequate measurement of the quality of care delivered nationwide and benchmark the clinical management of nAMD at a country level compared to other real-world international cohorts.

KEYWORDS
aflibercept, age-related macular degeneration, audit, benchmark standard, bevacizumab, national database, national dataset, neovascular AMD, ranibizumab

1 | INTRODUCTION

There is a growing interest for anti-VEGF therapy outcomes from routine clinical practice. In neovascular age-related macular degeneration (nAMD), the broader criteria for eligibility of treatment compared with randomised clinical trials (RCT) and the potential for undertreatment may result in lower visual gains.[1] In the last decade, the evolution of treatment regimens such as fixed bimonthly (FB) or treat-and-extend (TAE) have heavily influenced the treatment guidelines worldwide.[2] Meanwhile most of the RCT employed monthly and bimonthly treatment regimens, real world-studies transitioned from pro-re-nata (PRN) approaches to the adoption of pro-active regimens with TAE or FB injections, a paradigm shift that was reflected in significant improvements in routine clinical care outcomes.[1] Recently, several trials have compared the clinical outcomes of fixed dosing with TAE regimens, that are being adopted by many physicians worldwide for its potential to reduce the treatment burden while maintaining an adequate control of the disease.[3,4]

In parallel, the advent and development of electronic medical records (EMR) systems has allowed data from multiple centres to be collated.[5–7] In the last decade, two EMR systems and one online based-tool have reported valuable information about real-world AMD clinical outcomes. The use of a single EMR software was used in the United Kingdom to create the AMD EMR dataset that provided data from over 22.000 patients.[7] In the United States, the Intelligent in Sight Registry (IRIS) gathered data from over 14.000 nAMD patients.[8] Finally, the Fight Retinal Blindness (FRB!) registry has collated data from 7000 patients in Australia, New Zealand and Switzerland.[9,10] These three approaches have provided the largest evidence proof of real-world clinical outcomes of anti-VEGF therapies, including visual outcomes, the optimum treatment regimens, the results of switching drugs, the time to lesion inactivation, the intercentre variability or the involvement and outcomes of treated fellow eyes.[1,5–7,10–13]

However, very few studies have reported specifically outcomes at a national level in an individual country. This is a significant factor, as the environment in which anti-VEGF therapy is applied varies considerably between countries due to factors such as the presence of a public national health service or a private practice system, treatment access, drug reimbursement schemes and regulatory issues that ultimately depend on national bodies, as well as adherence to national colleges or clinical societies guidelines.[14,15] Very few national datasets have been published on this topic in a multicentre setting, and most of them were carried out in the PRN regimen era.[16–20]

In Spain, data about AMD real world outcomes are scarce. There is only one previous multicentric report in the PRN era in 2013, which clearly reported undertreatment in a small series of 12 selected centres,[21] and few small single centre series that presented data with FB and TAE regimens.[22–25] For these reasons, no information is available about the visual outcomes and treatment frequency achieved with proactive regimens nationwide in Spain, as no multicentric studies have been previously conducted in routine clinical care.

The aim of this project is to collate a national dataset of nAMD eyes treated with anti-VEGF drugs in Spain, using an international consortium health outcomes measurement (ICHOM)-compliant validated online web-based tool, the FRB! nAMD module, to audit the clinical outcomes at a national level and benchmark our performance with other international studies.

2 | METHODS

2.1 | Study design, setting and ethics approval

National, multicentre, observational study. The Spanish drug agency (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS) classified the study as a

prospective follow-up post-authorization study (EPA-SP) (27th June 2018), and ethics approval was obtained from the coordinating centre Institutional Review Board (IRB) (HCB/2018/0123). All local approvals were obtained from the local authorities (July 2019–March 2020). A total number of geographically diverse 28 hospitals were granted with licences to use the online platform, data extraction was performed by 26th April 2020 and data were delivered to the analysis team by May 2020. The study adhered to the tenets of the Declaration of Helsinki and followed the STROBE checklist for reporting observational studies. All patients in ongoing treatment provided their written informed consent.

2.2 | Variables

Analysis was restricted to eyes undergoing intravitreal therapy with anti-VEGF drugs for nAMD (i.e., ranibizumab, aflibercept, bevacizumab). Data entry was performed using an electronic web-based online platform, the FRB! AMD module.[26] This electronic form has a structured dataset that allows rapid pooling of the data fields collected, including VA for each eye, choroidal neovascularization (CNV) lesion activity and treatment details (i.e., drug) and complications. Post-operative local and systemic complications fields were also collected. Patient reported outcome measures (PROMs) electronic questionaires were also available to participating centres (not analysed in this report).

2.3 | Data sources/measurements

Demographics included age, sex, ethnicity and smoking habit. Ocular data included phakic status, previous ocular surgery, previous treatments and ocular comorbidities. The best-measured VA was expressed as Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR letters at all time points. Analysis for eyes with very low VA was undertaken by substituting counting fingers (CF), hand movement (HM), and perception of light (PL) with 2.0, 2.3, and 2.7, respectively.[27] Eyes with previous vitrectomy surgery or steroid injections were excluded. For subgroup analysis, we defined two non-overlapping participant groups, "treatment naïve" (TN) including eyes with no previous treatments for nAMD, and "previously treated" (PT) including eyes that received any previous intravitreal injection (i.e., previous anti-VEGF treatment) prior to the baseline visit.

2.4 | Statistical methods

Baseline and demographic characteristics were summarised with percentages for categorical variables, and mean, standard deviation (SD), median, first and third quartiles (Q1, Q3) for continuous variables. Observations began at the first treatment visit and continued until the 12-month visit (365 ± 30 days) or the last observed visit if they did not complete 12 months of follow-up. Subgroup analysis (TN vs. PT eyes) were performed with t-tests, Wilcoxon rank sum tests, Chi-square tests and Fisher's exact tests, where appropriate. Crude visual and anatomic outcomes used the last observation carried forward (LOCF) for non-completers.

Locally weighted scatterplot smoothing (LOESS) curves were used to visualise longitudinal trends in VA. Additionally, generalised additive mixed effects models were used to analyse longitudinal trends in VA including data from non-completers (predicted VA). Number of injections and visits were compared between TN and PT eyes with generalised Poisson mixed models with an offset for log days of follow-up. Kaplan–Meier survival curves were generated for time to non-completion and first physician grading of CNV inactivity. Analysis was performed in R version 4.0.0 (cran.r-project.org) utilising the glmmTMB (1.0.1) and mgcv (V1.8-31) packages for generalised linear and generalised additive mixed models, respectively. The survival (3.1-12) package was used to generate the Kaplan–Meier curves.

3 | RESULTS

From 16 786 eyes included in the FRB system, 3053 eyes were included in 28 participant centres in Spain and 1273 eyes (1014 patients) initiated treatment in the predefined timeframe to allow 24 months of follow up (prior to February 2018), being 971 eyes (76.2%) treatment naïve and 302 previously treated (23.7%) (Supporting information S1). Participant centres were predominantly public (82.1%, 23/28). The treatment regimens used after the three-monthly loading dose injections were FB and TAE. Demographics and clinical characteristics of study eyes are presented in Supporting information S2. Two study cohorts were defined as per the completed follow up period, 12 months (n = 1148, 90.2%) and 24 months (n = 876, 68.8%). Subgroup analysis was performed by TN and PT eyes in both study cohorts.

3.1 | Visual acuity outcomes

Visual outcomes in both study cohorts are presented in Table 1 and Figure 1. In the 12 months completers cohort, mean baseline and final VA (mean ± standard deviation, SD) was 57.7 ± 19.6 and 60.9 ± 20.3 letters, respectively, with significant differences between TN and PT eyes at baseline VA (56.6 ± 20.1 vs. 61.2 ± 17.5,

TABLE 1 Clinical outcomes of study eyes

Time point	Outcome	All eyes	Pre-treated	Treatment-naive	*p* Value
12 months	Completers, *n* (%)	1148 (90.2%)	275 (91.1%)	873 (89.9%)	
	Baseline VA				
	Mean (SD)	57.7 (19.6)	61.2 (17.5)	56.6 (20.1)	**<0.001**
	Final VA				
	Mean (SD)	60.9 (20.3)	61.3 (18.5)	60.8 (20.8)	0.702
	VA <35, %				
	Baseline/% final	15.4%/13.6%	10.9%/12%	16.8%/14.1%	
	VA ≥70, %				
	Baseline/% final	35.2%/45.5%	42.9%/43.6%	32.8%/46%	
	VA change				
	Mean (95% CI)	3.2 (2.2, 4.1)	0.1 (−1.4, 1.5)	4.2 (3, 5.3)	**<0.001**
	VA change, % loss/% gain				
	≥5 letters	24.7%/43.6%	26.5%/30.2%	24.2%/47.8%	0.32/**<0.01**
	≥10 letters	15.2%/29.4%	15.6%/17.1%	15.1%/33.2%	0.78/**<0.01**
	≥15 letters	11.2%/20.4%	10.9%/9.5%	11.3%/23.8%	1.0/**<0.01**
	Active visits, %	55.8%	59.8%	54.4%	**0.004**
	Injections, median (Q1, Q3)	7 (5, 8)	6 (5, 8)	7 (6, 8)	**0.002**
	Bevacizumab, %	23.8%	14%	26.7%	
	Ranibizumab, %	39.1%	38.7%	39.3%	
	Aflibercept, %	37.1%	47.2%	34.1%	
	Visits, median (Q1, Q3)	9 (8, 11)	8 (7, 11)	9 (8, 11)	**<0.001**
24 months	Completers, *n* (%)	876 (68.8%)	223 (73.8%)	653 (67.3%)	
	Baseline VA				
	Mean (SD)	58.7 (19)	62.2 (17)	57.5 (19.5)	**<0.001**
	Final VA				
	Mean (SD)	60 (21.1)	58.8 (21.1)	60.4 (21.2)	0.326
	VA ≤35, %				
	Baseline/% final	14%/15.5%	10.3%/16.6%	15.3%/15.2%	
	VA ≥70, %				
	Baseline/% final	37.2%/45.4%	44.4%/40.8%	34.8%/47%	
	VA change				
	Mean (95% CI)	1.3 (0.1, 2.5)	−3.4 (−5.6, −1.2)	2.9 (1.5, 4.4)	**<0.001**
	VA change, %				
	Loss/% gain				
	≥5 letters	31.2%/40.6%	38.1%/26.9%	28.8%/45.3%	**<0.01**/**<0.01**
	≥10 letters	21.1%/26.9%	24.7%/14.3%	19.9%/31.2%	0.10 /**<0.01**
	≥15 letters	14.8%/21.1%	15.7%/10.3%	14.5%/24.8%	0.64/**<0.01**
	Active visits, %	55%	58.2%	53.9%	0.057
	Injections, median (Q1, Q3)	11 (9, 14)	11 (9, 14)	11 (8, 14)	0.329

$p < 0.001$) but not at 12 months VA (60.8 ± 20.8 vs. 61.3 ± 18.5, $p = 0.702$). Mean VA change (mean, 95% confidence interval, CI) was +3.2 letters in the overall cohort (95% CI +2.2, +4.1), again with significant differences between TN (+4.2 letters, 95% CI +3, +5.3) and PT eyes (+0.1 letters, 95% CI −1.4, +1.5; $p < 0.001$). At

TABLE 1 (Continued)

Time point	Outcome	All eyes	Pre-treated	Treatment-naive	*p* Value
	Bevacizumab, %	19.3%	10.3%	22.3%	
	Ranibizumab, %	39.5%	36.3%	40.5%	
	Aflibercept, %	41.2%	53.5%	37.2%	
	Visits, median (Q1, Q3)	15 (13, 20)	14 (12, 18)	16 (13, 20)	**0.001**

Note: Visual outcomes, number of injections, number of visits and percentage of visits with active lesions at 12 and 24 months for all eligible eyes, treatment-naïve and pre-treated eyes completing 12 and 24 months of treatment, respectively. *p* Values are comparing pre-treated and treatment-naïve eyes. Significant *p* values are highlighted in bold.

Abbreviations: CI, confidence interval; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); SD, standard deviation; VA, visual acuity.

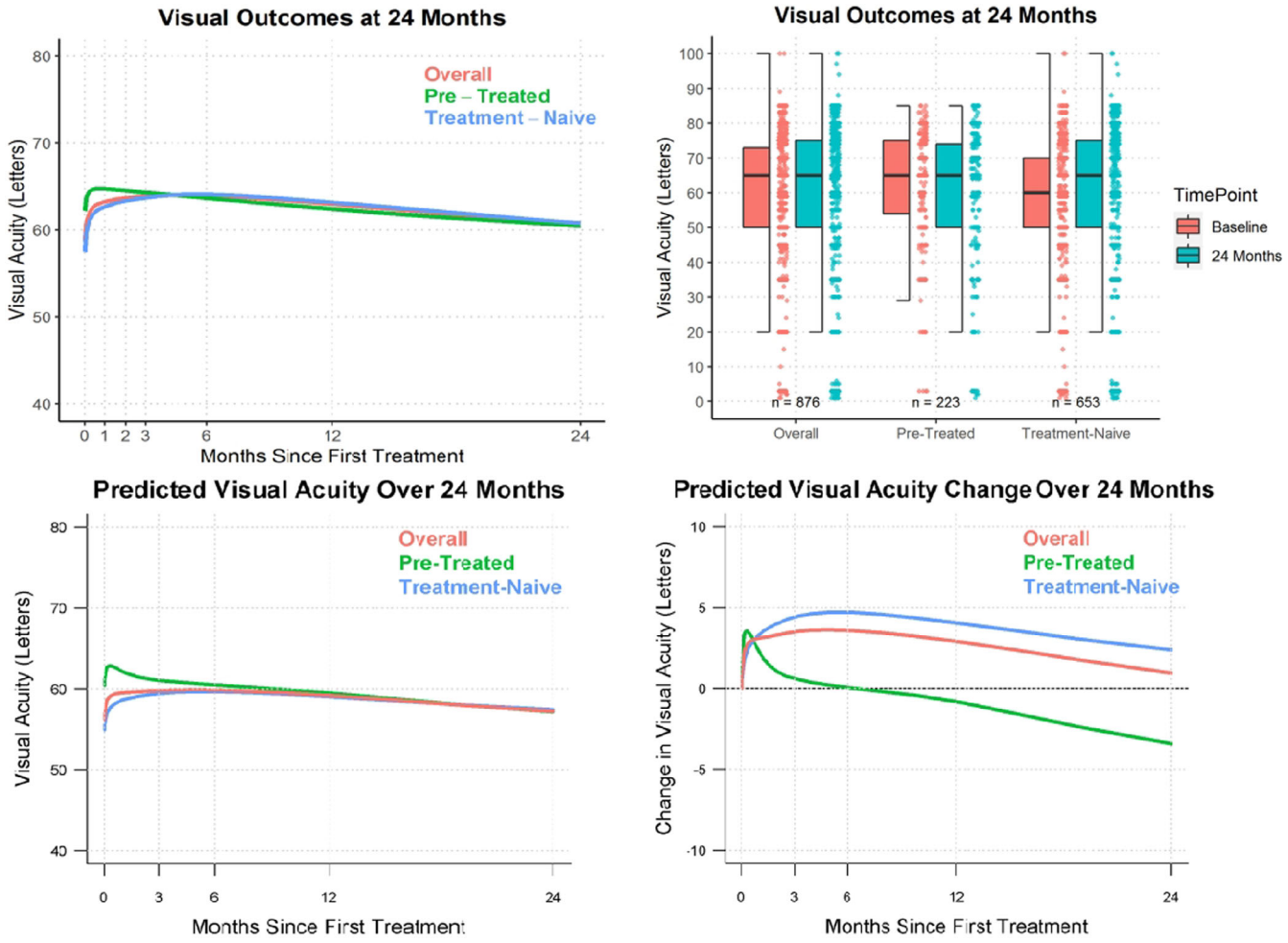

FIGURE 1 Visual outcomes at 24 months. Mean visual acuity (Top-left). Locally weighted scatterplot smoothing (LOESS) regression curve of mean visual acuity over 24 months of treatment for all 24-month completers (overall), treatment-naïve eyes, and previously treated eyes. Treatment-only visits were excluded from the model. Distribution of eyes by visual acuity levels and subgroup analysis by naïve and previously treated eyes cohorts (Top-right). Hybrid boxplot of visual outcomes at 24 months for all 24-month completers (overall), treatment-naïve eyes, and previously treated eyes. The whiskers represent the 25th and 75th quartiles plus or minus the interquartile range. Each dot represents an individual eye. Predicted visual acuity (bottom-left) and visual acuity change (bottom-right). Longitudinal generalised additive models for predicted visual acuity (A) and predicted visual acuity change (B) over 24 months of treatment for all eyes (overall), treatment-naïve eyes, and pre-treated eyes. Models included longitudinal data from completers and non-completers. Treatment-only visits were excluded from the model. The predicted mean (95% CI) change in visual acuity at 24 months when data from completers and non-completers were included was +0.9 (−0.1, 2.0) letters overall, +2.4 (1.3, 3.5) letters for treatment-naïve eyes, and −3.4 (−5.4, −1.4) letters for previously treated eyes

12 months, the percentage of 15-letters gainers/losers was 20.4%/11.2% in the overall cohort, 23.8%/11.3% in TN and 9.5%/10.9% in PT eyes.

In the 24 months completers cohort, mean baseline and final VA was 58.7 ± 19.0 and 60.0 ± 21.1, with significant differences between TN and PT eyes in baseline VA (57.5 ± 19.5 vs. 62.2 ± 17.0, $p < 0.001$) but not in final VA. Figure 1 shows the mean VA regression curve over 24 months (top left), and the distribution of eyes at baseline and at 24 months for the overall, TN and PT cohorts (top right). Mean VA change at 24 months was +1.3 letters (95% CI +0.1, +2.5) in the overall cohort, and significant differences were observed between TN (+2.9 letters, 95% CI +1.5, +4.4) and PT eyes (−3.4 letters, −5.6, −1.2; $p < 0.001$). At 24 months, the percentage of 15-letters gainers/losers was 21.1%/14.8% in the overall cohort, 24.8%/14.5% in TN and 10.3%/15.7% in PT eyes.

Finally, longitudinal generalised additive models were created to estimate the predicted VA and VA change over 24 months for the overall, TN and PT eyes cohorts, including data from completers and non-completers (Figure 1, bottom left and bottom right). In this analysis, the mean VA change in visual acuity at 24 months was +0.9 letters (95% CI −0.1, 2.0) in the overall cohort, +2.4 (95% CI 1.3, 3.5) letters for TN eyes, and −3.4 letters (95% CI −5.4, −1.4) letters for PT eyes.

3.2 | Number of injections, number of visits, lesions activity and study drugs

In the 12 months completers cohort, the median (Q1, Q3) number of injections was seven injections[5,8] in the overall cohort and was significantly greater in TN eyes ($7^{6,8}$) than PT eyes ($6^{5,8}$; $p = 0.002$). Similarly, the median (Q1, Q3) number of visits was $9^{8,11}$ in the overall cohort and was significantly greater in TN eyes ($9^{8,11}$) compared to PT eyes ($8^{7,11}$; $p < 0.001$).

In the 24 months completers cohort, the median (Q1, Q3) number of injections was $11^{9,14}$ injections in the overall cohort and no differences were observed between TN ($11^{8,14}$) and PT eyes ($11^{9,14}$; $p = 0.329$). The median (Q1, Q3) number of visits was 15,[13,20] with significant differences between TN ($16^{13,20}$) and PT ($14^{12,18}$) eyes ($p < 0.001$).

The percentage of visits with active lesions at 12/24 months was 55.8%/55%, and this was significantly lower in TN versus PT eyes at 12 months (54.5% vs. 59.8%, $p = 0.004$) but not at 24 months (53.9% vs. 58.2%, $p = 0.057$). The median time to first grading of lesion inactivity was 117 days (IQR 191), with no significant differences between TN eyes and PT eyes. No differences were observed in the survival analysis of time to first grading of lesion inactivity (Supporting information S3).

3.3 | Outcomes for non-completers

There were 397 eyes (31.2%) that did not complete 24 months follow up, of which 318 eyes were TN (32.7%) and 79 eyes were PT eyes (23.2%). The median follow up of non-completers was 425 days (IQR 292) (Supporting information S4), and at the time of dropout these eyes received a median number of seven injections (IQR 5) and a median number of nine visits (IQR 5). The mean (±SD) baseline and final VA of these eyes was 50.8 ± 23.8 and 50.6 ± 28.3, with a mean VA change of −0.1 letters (95% CI −2.1, +1.8). The most frequent physician-reported reasons for study drop out prior to completing 24 months of follow up were patient deceased ($n = 14$, 3.5%), further treatment considered futile ($n = 74$, 18.6%), medically contraindicated treatment ($n = 7$, 1.8%), patient declining treatment ($n = 11$, 2.8%), patients going to another doctor ($n = 5$, 1.3%), treatment considered successful ($n = 56$, 14.1%) and unknown reason ($n = 230$, 57.9%). A description of the clinical outcomes of non-completers is detailed in Supporting information S5.

4 | DISCUSSION

This is the largest nAMD study ever conducted in Spain to evaluate the clinical outcomes of anti-VEGF therapy at a national level. The baseline characteristics, visual outcomes, number of injections and number of visits reported in this study provide a realistic estimation of how nAMD is managed in our country. The results described here are comparable to other real-world international cohorts and represent an adequate measurement of the quality of care delivered nationwide in the participant centres.

The visual outcomes reported in this series are in line with other national cohorts that evaluated pro-active treatment regimens such as TAE or FB, and although direct comparisons cannot be made, overall are better than those reported in routine clinical care in the PRN era, especially in treatment naïve eyes (Tables 2 and 3),[7,10,15,28–32] and clearly worse than the TAE randomised clinical trials (Table 4).[3,33–38] In the UK national AMD dataset, PRN regimens produced worse visual acuity outcomes with a lower number of injections but a greater number of visits at both 12 and 24 months (+2/−2 letters, 5.7/9.4 injections and 9.2/17.4 visits).[5] Most other national cohort data have been reported as 12 months outcomes of PRN regimens. In Germany, the WAVE study[16] reported worse visual gains (+0.02 vs. +3.2 letters in our 12-month cohort) with fewer injections (4.34 vs. 7). The LUMIERE[17] and TWIN[18] studies from France reported similar VA gains (+3.2 and +4.3) again with

TABLE 2 Summary of national AMD datasets clinical outcomes (cohorts with $n > 100$ eyes)—12 months results

Studies	Year	Country	Drug type	Regimen	Eyes	Centers	*N*	Baseline VA	VA gain	Injections	Visits	Follow-up
12 months												
LUMIERE study—Cohen et al.	2013	France	RBZ	PRN	TN + PT	7	551	53.2	+3.2	5.1	8.6	12 months
UK-EMR—Tufail et al.	2014	UK	RBZ	PRN	TN	14	8598	55	+2	5.7	9.2	12 months
Swedish MR—Westborg et al.	2014	Sweden	RBZ/AFB	PRN	TN + PT	-	3509	62.0	+1.9	6.1	-	12 months
UK-EMR—Talks et al.	2015	UK	AFB	F	TN	14	1840	53.7	+5.1	7	7.3	12 months
TWIN study—Souied et al.	2015	France	RBZ	PRN	TN + PT	-	881	56.8	+4.3	5.6	7.4	12 months
AURA study**—Holz et al.	2016	All countries	RBZ	PRN	TN	-	1695	55.4[A]	+2.4	5.4	5.8	12 months
		France				-	340	56.0	+0.8	4.6	4.9	
		Germany				-	232	52.9	+1.1	4.8	5.1	
		Canada				-	149	47.2	+3.2	6.8	7.7	
		UK				-	396	55.0	+6.0	5.9	6.2	
		Italy				-	272	65.5	0	4.0	4.2	
		Netherlands				-	258	50.1	+3.8	6.8	7.1	
WAVE study—Finger et al.	2017	Germany	RBZ	PRN	TN + PT	274	3470	53	+1*	4.3	-	12 months
Jaki-Mekjavić etal	2018	Slovenia	AFB	T&E	TN	4	115	57.9	+6.5	8.4	8.8	12 months
LUMINOUS study—Holz et al.	2019	All countries	RBZ	PRN	TN	-	3379	51.9	+3.1	5.0	8.8	12 months
		Russia				20	382	42.1	+1.6	2.7	-	
		Poland				15	298	46.5	+3.0	4.0	-	
		Canada				18	376	48.3	+2.5	7.5	-	
		Germany				18	128	53.3	+2.3	5.2	-	
		Australia				21	158	52.9	+4.5	8.7	-	
		UK				49	746	56.3	+2.7	5.5	-	
		Slovakia				12	293	56.6	+2.5	5.6	-	
		Japan				91	406	57.6	+6	0	4.0	-
SIERRA-AMD—Khanani et al.	2020	USA	RBZ/AFB/BEV	F/T&E	TN + PT	58	32840	53.1	+1.1	7.6	9.2	12 months
In-EYE[C] trial—Lopez-Galvez et al.	2020	Spain	RBZ	PRN	TN	31	104	56.7	+7.3	7.4	13.6	12 months
				FB			103	59.2	+7.0	7.6	8.6	
				T&E			99	54.8	+6.7	9.3	10.4	
THIS STUDY—FRB Spain (Zarranz-Ventura et al. 2022)	**2022**	**Spain**	**RBZ/AFB/BEV**	**F/T&E**	**TN + PT**	**28**	**1148**	**57.7**	**+3.2**	**7[B]**	**9[B]**	**12 months**
					TN		**873**	**56.6**	**+4.2**	**7**	**9**	
					PT		**275**	**61.2**	**+0.1**	**6**	**8**	

Note: *Converted from LogMAR scale, **AURA was conducted in eight countries: France, Germany, Canada, UK, Italy, the Netherlands, Ireland and Venezuela. The last two are not included in the table as per their national cohort size ($n < 100$ eyes), [A]baseline VA in the overall cohort, [B] median, [C] the In-EYE Trial is not a routine clinical care study, it is a national clinical trial included in the table for outcome comparison purposes].

Abbreviations: AMD, age-macular degeneration; AFB, aflibercept; F, fixed; TN, treatment naïve; PRN, pro-re-nata; PT, previously treated; RBZ, ranibizumab; RL, real-life; T&E, treat-and-extend; VA, visual acuity.

TABLE 3 Summary of national AMD datasets clinical outcomes (cohorts with n>100 eyes)—24 months results

Studies	Year	Country	Drug type	Treatment regimen	Eyes	Centers	*N*	Baseline VA	VA gain	Injections	Visits	Follow-up
24 months												
UK-EMR—Tufail et al.	2014	UK	RBZ	PRN	TN	14	4990	55	+1	9.4	17.4	24 m
Casaroli-Marano et al.	2014	Spain	RBZ	PRN	TN	12	208	47.93	+3.13	6.1	9	24 m
FRB Australia—Arnold et al.	2015	Australia	RBZ /AFB	T&E	TN	-	1198	56.5	+5.3	13.0	14.6	24 m
AURA study*—Holz et al.	2015	All countries	RBZ	PRN	TN	-	1184	55.4[A]	+0.6	8.9	9.8	24 m
		France				-	240	56.0	+0.8	7.4	8.1	
		Germany				-	136	52.9	-0.8	7.2	8.1	
		Canada				-	107	47.2	+1.6	12.1	14.6	
		UK				-	350	55.0	+4.1	9.5	10.2	
		Italy				-	159	65.5	-2.9	6.2	6.7	
		Netherlands				-	163	50.1	+2.6	10.9	11.7	
*AURA study**—Ziemsen et at.*	*2015*	*Germany*	*RBZ*	*PRN*	*TN*	*28*	*420*	*52.9*	*-0.8*	*5.6*	*10.9*	*24 m*
*AURA study**—Van Asten et al.*	*2019*	*Netherlands*	*RBZ*	*PRN*	*TN*	-	*337*	*50.4*	*+2.6*	*8.8*	-	*24 m*
*AURA study**–Sivaprasad et al.*	*2016*	*UK*	*RBZ*	*PRN*	*TN*	*13*	*410*	*55.0*	*+4.1*	*9.0*	*18.4*	*24 m*
UK-EMR—Almuhtaseb et al.	2017	UK	AFB	FB	TN	17	1180	56.3	+2.3	11.3	12	24 m
Jaki-Mekjavić et al.	2018	Slovenia	AFB	T&E	TN	4	115	57.9	+7.0	6.1	6.4	24 m
SIERRA-AMD—Khanani et al.	2020	USA	RBZ/AFB/BEV	FB/T&E	TN + PT	58	17171	53.1	-1.3	14.3	17.5	24 m
THIS STUDY—FRB Spain (Zarranz-Ventura et al. 2022)	**2022**	**Spain**	**RBZ/AFB/BEV**	**FB/T&E**	**TN + PT**	**28**	**876**	**58.7**	**+1.3**	**11[A]**	**15[A]**	**24 months**
					TN		**653**	**57.5**	**+2.9**	**11**	**16**	
					PT		**223**	**62.2**	**-3.4**	**11**	**14**	

Note: *AURA was conducted in eight countries: France, Germany, Canada, UK, Italy, the Netherlands, Ireland and Venezuela. The last two are not included in the table as per their national cohort size ($n < 100$ eyes).
**Independent country publications from the AURA study. [A]Median.
Abbreviations: AMD, age-macular degeneration; AFB, aflibercept; FB, fixed bimonthly; TN, treatment naïve; PRN, pro-re-nata; PT, previously treated; RBZ, ranibizumab; RL, real-life; T&E, treat-and-extend; VA, visual acuity.

TABLE 4 Summary of treatment and extend regimen randomized clinical trials results in age-related macular degeneration at 12 and 24 months

Studies	Year	Drug type	Treatment regimen	Eyes	*N*	Baseline VA	VA gain	Injections	Visits
12 months results									
TREX—*Wykoff et al.*	2015	RBZ	Monthly vs. TAE	TN	60	60.5[A]	+9.2 vs. +10.5	13.0 vs. 10.1	-
TREND—*Silva et al.*	2018	RBZ	Monthly vs. TAE	TN	650	60.6 vs. 59.5	+7.9 vs. +6.9	11.1 vs. 8.7	-
CANTREAT—*Kertes et al.*	2019	RBZ	Monthly vs. TAE	TN	526	59.5 vs. 58.9	+6.0 vs. +8.4	11.8 vs. 9.4	-
ALTAIR—*Ohji et al.*	2020	AFB	TAE with 2 weeks vs. 4 weeks adjustments	TN	246	54.8 vs. 55.3	+9.0 vs. +8.4	7.2 vs. 6.9	-
ARIES—*Mitchell et al.*	2021	AFB	TAE with 2 weeks vs. 8 weeks adjustments	TN	271	60.2 vs. 61.3	+7.8 vs. +10.2	7.1 vs. 8.0	-
THIS STUDY—FRB Spain (Zarranz-Ventura et al. 2022)	**2022**	**RBZ/ AFB/BEV**	**Two monthly fixed/TAE**	**TN + PT**	**1148**	**57.7**	**+3.2**	**7[B]**	**9[B]**
24 months results									
TREX—*Wykoff et al.*	2016	RBZ	Monthly vs. TAE	TN	50	60.0[A]	+10.5 vs. +8.7	25.5 vs. 18.6	-
CANTREAT—*Kertes et al.*	2020	RBZ	Monthly vs. TAE	TN	466	59.4 vs. 59.6	+6.0 vs. +6.8	23.5 vs. 17.6	-
ALTAIR—*Ohji et al.*	2020	AFB	TAE with 2 weeks vs. 4 weeks adjustments	TN	246	54.8 vs. 55.3	+7.6 vs. +6.1	10.4 vs. 10.4	-
ARIES—*Mitchell et al.*	2021	AFB	TAE with 2 weeks vs. 8 weeks adjustments	TN	210	60.2 vs. 61.3	+4.3 vs. +7.9	12 vs. 13	-
THIS STUDY—FRB Spain (Zarranz-Ventura et al. 2022)	**2022**	**RBZ/ AFB/BEV**	**Two months fixed/TAE**	**TN + PT**	**876**	**58.7**	**+1.3**	**11[A]**	**15[A]**

Note: [A]Baseline VA in the overall cohort, [B]median.

Abbreviations: AMD, age-macular degeneration; AFB, aflibercept; TN, treatment naïve; PT, previously treated; RCT, randomized clinical trial; RBZ, ranibizumab; TAE, treat-and-extend; VA, visual acuity.

fewer injections (5.1 and 5.6) and visits (8.6 and 7.4) compared to our study (nine visits). The VA gains of patient cohorts may vary depending on the baseline VA and do not necessarily represent the quality of care delivered. Interestingly, the baseline VA observed in our cohort was higher than most of these series, which may reflect fewer delays in detecting and treating the disease, as well as less potential for VA gain due to a ceiling effect. In any case, the number of injections and visits reflect a less aggressive approach to treatment than the proactive regimen followed in our study cohort.

Our data are consistent with the few national reports of outcomes of proactive treatment regimens. Similar visual gains were observed at 12 and 24 months with a FB regimen in a national cohort study from the UK (+5.1 vs. +3.2 and +2.3 vs. +1.3 letters) with the same number of injections (7 vs. 7 and 11.3 vs. 11) and fewer visits (7.3 vs. 9 and 12 vs. 15).[7] In Australia, a TAE approach achieved better visual gains (+5.3 letters) with a higher number of injections and visits (13 and 14.6, respectively) at 24 months.[10] A recent report in the USA revealed worse visual outcomes (−1.3 letters) with more injections (14.3) and visits (17.5) at 24 months in a cohort of eyes predominantly treated with FB injections.[39] The apparently mediocre outcomes reported in the U.S. study, which had by far the largest numbers, may be affected by low-data quality with only 2/3 of eyes having an identifiable measurement of starting VA and a 1-year dropout rate of nearly 50%. These variations in outcomes from different regions may be related to differences in baseline VA, sample size and organisational issues including access to treatment in the different centres and countries. Overall, most of these series with these regimens report similar visual outcomes, generally with a greater number of injections and lower number of visits in TAE compared with FB regimens. Consistently with these considerations, the outcomes reported in this study suggest adequate management of nAMD nationwide in Spain in

terms of visual outcomes, number of injections and number of visits, and highlight the superior visual outcomes achieved with proactive TAE and FB regimens compared with previous reports of the outcomes of PRN regimens in real-world practice.[5,21]

The barriers for implementation of proactive regimens in routine clinical care have been thoroughly described.[1,40,41]A recent Spanish report identified healthcare overload, lack of human resources, healthcare coordination issues and prolonged waiting times to receive intravitreal therapy.[42] Organisational problems, confusion over scheduling and healthcare resource availability were also identified as potential roadblocks for implementing proactive treatment regimens in real-world scenarios. Measures directed to solve administrative and managerial issues can be effectively implemented in single centres, as described in recent reports with adequate results, the challenge is to scale these measures nationwide in a multicentre setting.[22–25] This may be one of the reasons why real world multicentric studies underperform compared to clinical trials even with fixed regimens (i.e., +5.1 vs. +8.4 letters at 12 months in the UK aflibercept cohort).[7] Consistent with this, a recent Spanish clinical trial that compared the efficacy of different treatment regimens also found greater visual gains than we have presented here.[4]

The collation of large national datasets has been possible due to the development of adequate information technology tools, such as EMR softwares or online web-based tools, being systems that present considerable differences between them. EMR systems need local structural support, are most costly and often require the installation of a software package locally in the centres, which ultimately needs to be linked to the general hospital EMR used by other specialties outside ophthalmology. This often represents a roadblock for implementation, as the boards of many centres adopt different EMRs. Ultimately, this duplication of EMRs can often be solved with specially designed interfaces to link and integrate data between both softwares, but this commonly requires additional funding representing an extra problem for the international expansion of these systems, especially in countries which are transitioning to EMR. Conversely, web-based systems are easier to implement internationally as only an internet connection is required, with the disadvantages of requiring manual entry of data or the previously discussed export interfaces for automated data entry in the system. The implementation of the FRB! system in Spain has been possible because it allows data entry using an internet connection without requiring installation of EMR software.

This study has a number of strengths and limitations. The large sample size, the collection of an ICHOM-compliant standardised minimum dataset using a web-based tool, the reflection of routine clinical care and the large number of centres are the strengths of this study. Its weaknesses include the use of off label medications in a fifth of the sample (19.3% bevacizumab in 24 months completers), and the loss to follow up of significant numbers of patients over time (9.8% at 12 months, 31.2% at 24 months). Whereas the first item reflects the local policies of some of the participating centres, the second is inevitable in a real-world clinical setting especially for studies over several years. Most other national studies have only reported 12-month outcomes. For this reason, to allow comparisons with other countries we present the clinical outcomes disclosed in two cohorts for 12- and 24-months completers, to benchmark our results internationally. A detailed analysis of the clinical outcomes of the non-completers cohort has been included (Supporting information S5). In this cohort, the median number of injections and visits at 12 months were consistent with the overall cohort (7 and 9, respectively), suggesting that the reasons for dropping out appear unrelated to the course of the treated disease.

In conclusion, this study, the largest ever conducted in Spain in nAMD, provides valuable data at a national level on routine clinical care. It demonstrates that independent high quality, large-scale national audits are feasible if committed health care professionals are provided with efficient IT systems to do them. The results reported in this study reflect an adequate management nationwide and benchmark the quality of care dispensed in the participating centres. This data is helpful to guide discussions on service delivery and support the implementation of measures directed to reduce the barriers to providing adequate, proactive treatment of nAMD in routine clinical practice.

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CONFLICT OF INTEREST

Javier Zarranz-Ventura and Mark C. Gillies receive funding and consult for Novartis Pharmaceuticals and Bayer.

AUTHOR CONTRIBUTIONS

Javier Zarranz-Ventura designed the study, conducted the research, analysed and interpreted data, wrote the manuscript and is the main director and the national coordinator of the FRB! Spain project. Alba Parrado-Carrillo, Marc Figueras-Roca and Ricardo P. Casaroli-Marano collected data and edited the manuscript. Vuong Nguyen performed the statistical analysis. Mark C. Gillies is one of the inventors of the software and edited the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX 1

FIGHT RETINAL BLINDNESS SPAIN users group (by center: Principal investigator and collaborators)

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26. **Hospital do Meixoeiro, Vigo:** Marta Rodríguez-Núñez, Ana Campo Gesto
27. **Clínica Rementería, Madrid**: Jesús Pareja Esteban, María del Pilar Ruiz del Tiempo
28. **Hospital Universitario Virgen del Rocio, Sevilla:** Mariano Rodríguez-Maqueda, María Angeles Espiñeira Periñan, Magdalena Sotomayor Toribio