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ORIGINAL RESEARCH

Treatment Regimens with Ranibizumab in Neovascular Age-Related Macular Degeneration: Real-World Results from the PACIFIC Study

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Introduction: Intravitreal anti-VEGF is the gold standard for treating neovascular age-related macular degeneration (nAMD). The treatment success depends not only on drug efficacy but also on regimen feasibility for physicians and patients. The implementation of different regimen might lead to varying outcomes. "Treat-and-extend" aims to minimize undertreatment with injections at each visit and tailored intervals. This study investigates the utilization and effectiveness of ranibizumab in nAMD, focusing on different treatment regimens in real-world settings.

Materials and Methods: The PACIFIC study, a non-interventional, prospective, multicenter study, included nAMD patients treated with ranibizumab at 185 sites across Germany, the Netherlands and Switzerland. Over 24 months, functional and morphological outcomes were documented for 3051 patients over 24 months, highlighting the practiced treatment regimens.

Results: A pattern of an observational approach with nevertheless increasing interval extension prevailed (70.4%, 1028 pre-treated; 68.6%, 1090 treatment-naïve patients), emerging as the preferred strategy within the first 3 months. Across all regimens, the average number of injections was comparable (mean ± SD: 7.34 ± 5.30 in pre-treated; 7.26 ± 4.70 in treatment-naïve patients). The treat and extend regimen, however, demonstrated superior effectiveness in improving visual acuity, particularly among treatment-naïve patients (number of injections: 7.89 ± 5.54 pre-treated; 9.54 ± 5.42 treatment-naïve patients).

Conclusion: Over 2-year observational period, the treat and extend regimen emerged as a highly effective approach, particularly for those newly diagnosed, with a low risk of undertreatment. Despite its benefits, an unconscious shift to a observe-and-extend or "monitor-and-extend" approach occurred early in treatment, highlighting the need for tailored approaches to optimize patient outcomes in clinical practice.

Keywords: anti-VEGF, visual acuity, treatment regimen, functional outcome, real-world results

Introduction

The leading cause of blindness in industrialized countries, and the third leading cause of blindness worldwide, is age-related macular degeneration (AMD).[1] Advanced AMD is divided into aggressive wet AMD (also called neovascular AMD [nAMD]) and slow but steadily progressing dry AMD, which ultimately leads to retinal atrophy.[2,3] While therapeutic options are limited for the treatment of dry AMD,[3] the standard treatment for wet AMD since first approval in the USA in 2006 is intravitreal anti-VEGF which acts to reduce fluid (serum and/or blood) accumulating in the macula due to choroidal neovascularization.[4] Anti-VEGF agents include pegaptanib,[5] ranibizumab,[6] aflibercept,[7] brolucizumab,[8] faricimab,[9,10] and bevacizumab (off label).[11] Clinical trials[12,13] and real-world studies[14,15] have shown efficacy of ranibizumab treatment in nAMD and confirmed effectiveness in routine clinical practice. However, methodological

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limitations in real-world studies prevent the implementation of treatment protocols or monitoring, with studies reporting low mean numbers of injections and the potential undertreatment of some patients.[16]

A treatment regimen that can be easily implemented by both clinicians and patients is fundamental to achieving optimal functional and morphological outcomes. Anti-VEGF therapies can be applied according to regimens that differ fundamentally in terms of diagnostic and application intervals. Known examples of regimens include fixed application intervals,[12] applications on demand (*pro re nata*), and treat and extend regimens[17] which allow for a variation in treatment interval based on the disease activity of the patient. German guidelines recommend *pro re nata* treatment or the treat and extend regimen.[18] "Treat-and-extend" aims to minimize undertreatment with injections at each visit and tailored intervals. In contrast, "observe-and-extend"[19] or "monitor-and-extend"[20] have been described. However, such a hesitant or wait-and-see approach may only be appropriate for low activity, complete fluid resorption and a low risk of recurrence.

The treatment regimens for anti-VEGF therapies have been introduced with varying degrees of success. Regular intravitreal injections are considerably stressful for patients[21] and often lead to poor functional outcomes in practice due to suboptimal adherence, while a treat and extend regimen may offer a more favorable balance between clinical outcomes and treatment burden.[22,23] The aim of the PACIFIC study was to describe the current status of ranibizumab therapy, with a focus on treatment regimens. Treatment, diagnosis, and therapy monitoring were performed according to routine clinical practice and at the investigator's discretion.

Materials and Methods

Study Design

The study was an observational, prospective, multicenter study in patients with nAMD in Germany, the Netherlands, and Switzerland who were treated with ranibizumab. Patients were enrolled across 185 sites from June 2015 until March 2019 with an observational period of up to 24 months per patient. There were no imposed treatment protocols, diagnostic or therapeutic procedures, or visit schedules, however, a minimum of one follow-up visit was required. Most patients received treatment in one eye only.

This study was conducted in accordance with relevant guidelines and with the ethical principles laid down in the Declaration of Helsinki. The study documents were approved by the ethics committee responsible for the study site of the principal investigator (*Ethik-Kommission der Bayerischen Landesärztekammer*), as well as by local ethics committees in the Netherlands (METC [*Medisch Ethische Toetsings Commissie*] Brabant and CGR [*Codecommissie Geneesmiddelen Reclame*]) and in Switzerland (EKNZ [*Ethikkommission Nordwest- und Zentralschweiz*]). The trial was registered on clinicaltrials.gov (NCT04847895).

Subjects

Inclusion criteria were treatment with ranibizumab (as per summary of product characteristics) and written informed consent. Both treatment-naïve (untreated) and pre-treated patients were included in the study. Pre-treated patients previously received treatment with ranibizumab, other anti-VEGF drugs, photodynamic therapy, laser coagulation, or intravitreal corticosteroids prior to the start of the PACIFIC study. A total of 185 sites had at least one patient in the safety evaluation set (SES), with 4948 patients in the SES, while 182 sites had at least one patient in the full analysis set (FAS), with 4932 patients in the FAS for all indications. This publication focuses on nAMD patients, with 3051 patients in the FAS (1461 pre-treated patients and 1590 treatment-naïve patients).

Statistical Methods

Demographic and baseline disease characteristics were documented at the initial visit. At follow-up visits, best-corrected visual acuity (BCVA) examinations, optical coherence tomography (OCT) examinations, information on injections, treatment regimens, and adverse events (AEs) were documented. The decimal BCVA was collected and transferred into the EDTRS letter score. Prior/concomitant diseases and AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Statistics were performed using the software SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA). AEs were analyzed for the SES and all other analyses were performed for the FAS.

Performed treatment regimens were calculated based on documented visit time points and injection time points. Planned treatment regimens were documented by the physician. Treatment regimens included the following:

- Fixed regimen: The patient receives an initial series of usually three monthly anti-VEGF injections. After the initial phase, injections continue at fixed intervals (eg, every 4 or 8 weeks), even if no disease activity is detected on OCT scans.
- *Pro re nata*: The patient receives an initial series of usually three monthly anti-VEGF injections. This is followed by regular check-ups (OCT, funduscopy). If there is no disease activity (no fluid, no visual deterioration), no injection is given. If the disease reactivates, a new injection is given.
- "Treat-and-extend": The patient receives an initial series of usually three monthly anti-VEGF injections. Once wet AMD is stable (no fluid or disease activity on OCT), the interval between injections is gradually increased (eg, from 4 to 6 weeks, then to 8 weeks, etc). If stability continues, the interval can be further extended (eg, to 10 or 12 weeks). If fluid or other signs of disease activity reappear during an extension, the interval is shortened (eg, from 10 to 8 weeks). The last stable interval is then considered the optimal long-term treatment interval.

The following pattern was identified as "observe-and-extend" approach: After initial stabilization of the disease through anti-VEGF injections, this protocol involves regular monitoring of retinal status using OCT and visual acuity assessments. If no signs of disease activity (eg, fluid accumulation, vision loss) are detected, the intervals between follow-up visits and treatments are gradually extended. The aim is to minimize treatment burden while maintaining disease control. Reactivation of disease prompts re-initiation or intensification of therapy.

In the statistical analysis for PACIFIC, if an injection that was considered treat and extend by the physician was not given within a time interval of ± 7 days due to a delay in daily practice, the injection was categorized as "as needed" and the regimen was classified as observe and extend. The patterns were retrospectively assigned based on the treatment data and compared with the regimens intended ("planned") by the treating physicians (as documented in statements of intent).

Results

Baseline Characteristics

A total of 3054 patients with nAMD were enrolled in the PACIFIC study with 3051 patients included in the FAS. Among these, 1461 patients had previously received treatment, while 1590 patients were treatment-naïve. Most patients were from Germany (1276 pre-treated, 1465 treatment-naïve), followed by Switzerland (66 pre-treated, 123 treatment-naïve) and the Netherlands (119 pre-treated, 2 treatment-naïve). For most patients from Germany, OCT costs were covered as an individual health service at patients' own expense (35.9% of pre-treated, 52.6% of treatment-naïve patients) or by statutory health insurance (32.1% of pre-treated, 18.8% of treatment-naïve patients). The percentage of German patients with statutory health insurance was 84.7% (1081/1276 patients) among the pre-treated and 90.0% (1318/1465 patients) among the treatment-naïve patients.

Demographics and baseline disease characteristics are shown in Table 1. Key demographic and baseline parameters were similar for pre-treated and treatment-naïve patients. Slightly more patients in the PACIFIC study were female, the mean age was approximately 79.6 and 78.2 years, respectively, for pre-treated and treatment-naïve patients.

The mean baseline BCVA, measured as early treatment diabetic retinopathy study (ETDRS) letters, was 58.0 ETDRS letters for pre-treated compared to 54.0 ETDRS letters for treatment-naïve patients. The vast majority of patients (69.7% of the pre-treated and 83.1% of the treatment-naïve patients) had a baseline OCT examination, with a mean central retinal thickness of 311.0 µm for pre-treated and 373.3 µm for treatment-naïve patients. Pre-treated patients had fewer fluorescence angiography (FLA) examinations at baseline compared to treatment-naïve patients (27.2% vs 66.4%, respectively).

Most ophthalmological findings were similar between pre-treated and treatment-naïve patients. Fibrosis and atrophic areas were observed more often in pre-treated patients, while subretinal fluid, with and without foveal involvement, cystoid fluid with foveal involvement, cataract, and bleedings or punctate bleedings, were observed more often in treatment-naïve patients (Table 2).

Table 1 Demographics and Baseline Characteristics of Patients with nAMD, by Pre-Treatment Status (FAS)

Parameter	Pre-Treated N=1461	Treatment-Naïve N=1590
Demographics		
Sex, n (%)		
Male	605 (41.4%)	629 (39.6%)
Female	856 (58.6%)	961 (60.4%)
Age at initial study visit [years], mean (SD)	79.57 (7.98)	78.15 (8.40)
Height [cm], mean (SD)	167.42 (8.855)	167.05 (9.128)
Weight [kg], mean (SD)	74.557 (13.421)	75.763 (13.949)
BMI [kg/m^2], mean (SD)	26.53 (4.00)	27.12 (4.35)
Most commonly reported diseases from medical history, n (%)[a]		
Myocardial infarct	74 (5.07%)	69 (4.34%)
Apoplexy	71 (4.86%)	62 (3.90%)
Hypertonia[b]	699 (47.84%)	774 (48.68%)
Hyperlipidaemia[b]	141 (9.65%)	127 (7.99%)
Renal insufficiency[b]	41 (2.81%)	32 (2.01%)
Diabetes mellitus[b]	217 (14.85%)	262 (16.48%)
No risk factors	229 (15.67%)	295 (18.55%)
Unknown/Missing[c]	237 (16.22%)	218 (13.71%)
Other	460 (31.49%)	463 (29.12%)
Fitness to drive, n (%)		
NA/Missing[d]	487 (33.3%)	474 (29.8%)
Yes	594 (40.7%)	674 (42.4%)
No	380 (26.0%)	442 (27.8%)
Inability to drive caused by visual impairment, n (%)		
Missing	8 (2.1%)	6 (1.4%)
Yes	319 (83.9%)	367 (83.0%)
No	53 (13.9%)	69 (15.6%)
Baseline BCVA examination of study eye		
n	1405	1564
logMAR, mean (SD)	0.541 (0.387)	0.621 (0.408)
ETDRS letters, mean (SD)	58.0 (19.3)	54.0 (20.4)
Baseline OCT examination of study eye		
Baseline OCT examination, n (%)		
Yes	1019 (69.7%)	1322 (83.1%)
No	376 (25.7%)	243 (15.3%)
Unknown/Missing[c]	66 (4.5%)	25 (1.6%)
Baseline OCT: central retinal thickness [µm]		
n	948	1273
Mean (SD)	311.0 (110.6)	373.3 (138.9)
FLA examinations of study eye		
Baseline FLA examination, n (%)		
Yes	397 (27.2%)	1055 (66.4%)
No	1005 (68.8%)	519 (32.6%)
Unknown/Missing[c]	59 (4.1%)	16 (1.0%)

(*Continued*)

Table 1 (Continued).

Parameter	Pre-Treated N=1461	Treatment-Naïve N=1590
Both eyes treated on the same day	242 (32.7%)	153 (25.5%)
Treatment delay [days], mean (SD)	11.2 (16.2)	9.2 (14.0)

Notes: [a]Multiple responses were possible. [b]This disease from medical history was explicitly documented as ongoing at baseline for the majority of patients. [c]Data were either reported as unknown or not reported (missing). [d]This item was either not applicable (eg, no driver's license) or not reported (missing).
Abbreviations: BCVA, best-corrected visual acuity; BMI, body mass index; ETDRS, early treatment diabetic retinopathy study; FAS, full analysis set; FLA, fluorescence angiography; logMAR, logarithm of the minimum angle of resolution; nAMD, neovascular age-related macular degeneration; N, number of patients in analysis set; n, number of non-missing observations; OCT, optical coherence tomography; SD, standard deviation.

Table 2 Common (>10%) Ophthalmological Findings at Baseline, by Pre-Treatment Status (FAS)

Parameter n (%)	Pre-Treated N=1461	Treatment-Naïve N=1590
Subretinal fluid with foveal involvement	729 (49.90%)	983 (61.82%)
Subretinal fluid without foveal involvement	349 (23.89%)	548 (34.47%)
Cystoid fluid inclusion with foveal involvement	526 (36.00%)	690 (43.40%)
Cystoid fluid inclusion without foveal involvement	282 (19.30%)	334 (21.01%)
Diffuse retinal thickening	532 (36.41%)	597 (37.55%)
Fibrosis	278 (19.03%)	149 (9.37%)
Pigment epithelium detachment	534 (36.55%)	615 (38.68%)
Vitreous detachment	224 (15.33%)	216 (13.58%)
Atrophic areas	366 (25.05%)	280 (17.61%)
Druses	725 (49.62%)	819 (51.51%)
Bleeding or punctate bleeding	265 (18.14%)	511 (32.14%)
Lesion Diameter <= 1 mm	109 (7.46%)	170 (10.69%)
Lesion Diameter > 1 mm	223 (15.26%)	260 (16.35%)
Cataract	430 (29.43%)	553 (34.78%)

Note: Multiple responses were possible.
Abbreviations: FAS, full analysis set; N, number of patients in analysis set; n, number of non-missing observations.

Treatment Regimens

For pre-treated patients with nAMD *pro re nata* was the most commonly planned treatment regimen (37.0%), followed by fixed regimen (30.7%). For treatment-naïve patients with nAMD, fixed regimen was the most commonly planned treatment regimen (55.2%), followed by *pro re nata* (25.3%) (Table 3). For pre-treated patients, this was mainly due to the characteristics of the patient population from Germany as the distribution of treatment regimens differed considerably for patients from the Netherlands (5.0% *pro re nata* and 47.1% fixed regimen) and Switzerland (16.7% each for both *pro re nata* and fixed regimen). For treatment-naïve patients, the distribution of treatment regimens was more similar between study countries.

Number of Injections

Most pre-treated patients received the baseline injection only in the study eye (1337 patients, 91.5%); only few patients (124 patients, 8.5%) received treatment of both eyes. Over the course of the first study year, the pre-treated patients received a mean (±SD) number of 5.19 ± 2.97 injections with ranibizumab for the study eye, with a total mean number of 7.34 ± 5.30 injections over the entire 24-month observational period. The number of injections for pre-treated patients over the whole observational period according to treatment regime was 12.34 ± 5.29 for the "treat-and-extend" group, 4.94 ± 4.17 for the fixed regimen, 7.60 ± 4.88 for those treated with "observe-and-extend" pattern and 3.57 ± 2.85 for the *pro re nata* regimen.

Table 3 Planned Treatment Regimen at Baseline for Patients with nAMD, by Pre-Treatment Status and by Country (FAS)

	Total	Germany	Netherlands	Switzerland
Pre-Treated Patients with nAMD	**N=1461**	**N=1276**	**N=119**	**N=66**
Planned treatment regimen, n (%):				
FIX	449 (30.7%)	382 (29.9%)	56 (47.1%)	11 (16.7%)
PRN	540 (37.0%)	523 (41.0%)	6 (5.0%)	11 (16.7%)
T+E	257 (17.6%)	191 (15.0%)	39 (32.8%)	27 (40.9%)
O+E	213 (14.6%)	179 (14.0%)	17 (14.3%)	17 (25.8%)
Missing	2 (0.1%)	1 (0.1%)	1 (0.8%)	0 (0.0%)
Reason for choice of treatment regimen, n (%):				
Medical reasons	1384 (94.7%)	1217 (95.4%)	108 (90.8%)	59 (89.4%)
Compatibility with organization of practice/clinic[a]	50 (3.4%)	40 (3.1%)	10 (8.4%)	0 (0.0%)
Compatibility with availability of patient[b]	10 (0.7%)	4 (0.3%)	0 (0.0%)	6 (9.1%)
Patient's request	15 (1.0%)	14 (1.1%)	0 (0.0%)	1 (1.5%)
Other reason	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Missing	1 (0.1%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Treatment-naïve patients with nAMD	**N=1590**	**N=1465**	**N=2**	**N=123**
Planned treatment regimen, n (%):				
FIX	878 (55.2%)	840 (57.3%)	1 (50.0%)	37 (30.1%)
PRN	402 (25.3%)	380 (25.9%)	0 (0.0%)	22 (17.9%)
T+E	168 (10.6%)	135 (9.2%)	0 (0.0%)	33 (26.8%)
O+E	139 (8.7%)	107 (7.3%)	1 (50.0%)	31 (25.2%)
Missing	3 (0.2%)	3 (0.2%)	0 (0.0%)	0 (0.0%)
Reason for choice of treatment regimen, n (%):				
Medical reasons	1527 (96.0%)	1403 (95.8%)	2 (100%)	122 (99.2%)
Compatibility with organization of practice/clinic[a]	40 (2.5%)	40 (2.7%)	0 (0.0%)	0 (0.0%)
Compatibility with availability of patient[b]	10 (0.6%)	9 (0.6%)	0 (0.0%)	1 (0.8%)
Patient's request	7 (0.4%)	7 (0.5%)	0 (0.0%)	0 (0.0%)
Other reason	3 (0.2%)	3 (0.2%)	0 (0.0%)	0 (0.0%)
Missing	3 (0.2%)	3 (0.2%)	0 (0.0%)	0 (0.0%)

Notes: [a]This reason was mainly specified as "Limitation to dedicated injection day" or "Limited capacities for control visits" for pre-treated patients and as "Limitation to dedicated injection day" for treatment-naïve patients. [b]This reason was mainly specified as "Problems with traveling" or "General health status" for pre-treated patients and "Problems with traveling" for treatment-naïve patients.
Abbreviations: FAS, full analysis set; FIX, fixed regimen; O+E, observe and extend regimen; N, total number of patients; n, number of non-missing observations; nAMD, neovascular age-related macular degeneration; PRN, pro re nata regimen; T+E, treat and extend regimen.

Similarly, most treatment-naïve patients received the baseline injection only in the study eye (1474 patients, 92.7%); only few patients (116 patients, 7.3%) received treatment of both eyes. Over the course of the first study year, the treatment-naïve patients received a mean (±SD) number of 5.55 ± 2.66 injections with ranibizumab for the study eye, with a total mean number of 7.26 ± 4.70 injections over the entire 24-month observational period. The number of injections for treatment-naïve patients over the whole observational period according to treatment regime was 11.84 ± 5.21 for the "treat-and-extend" regimen, 7.18 ± 4.17 for the "observe-and-extend" pattern, 4.31 ± 2.75 for the fixed regimen, and 4.54 ± 3.23 for the *pro re nata* regimen. The number of injections for the total population over the entire observation period is driven by observational pattern and the treat and extend group, which were also documented most frequently over the second year of therapy. This corresponds to the treatment regimens shown in Figure 1.

The overall performed treatment approach was observational for the majority of nAMD patients (1028 pre-treated patients [70.4%] and 1090 treatment-naïve patients [68.6%]) which emerged as a trend after only 3 months (Figure 1A and B).

Visual Outcomes

For patients treated according to a strict "treat-and-extend" regimen over the observational period of 24 months, visual acuity increased consistently both for pre-treated (n=211 patients at baseline, n=33 patients at month 24; Figure 2A) and

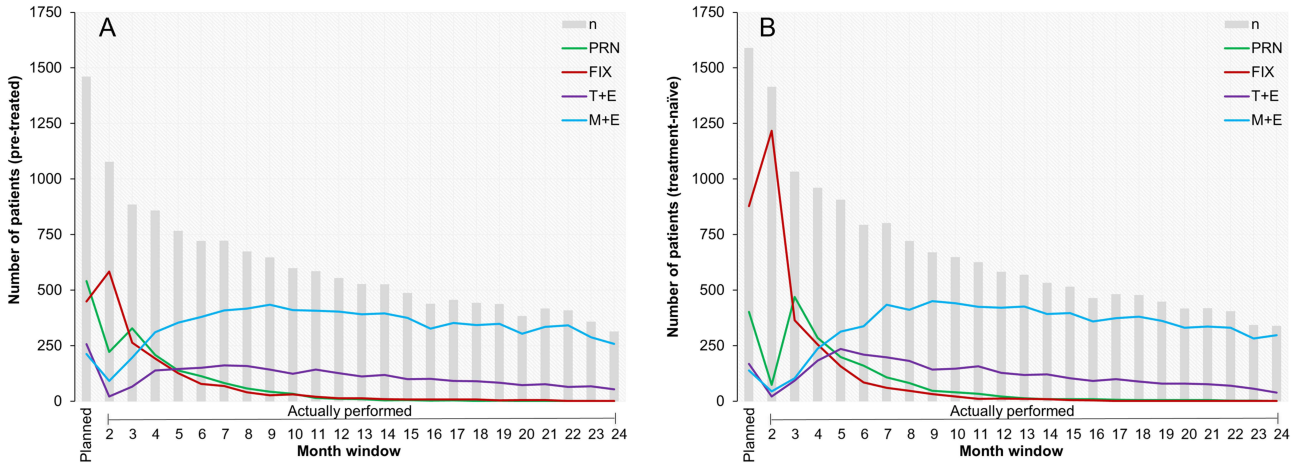

Figure 1 Treatment regimens over 24 months for pre-treated patients (**A**) and treatment-naïve patients (**B**) (FAS). Gray bars indicate number of patients with available data at each time point.
Abbreviations: FAS, full analysis set; FIX, fixed regimen; O+E, "observe- and- extend" pattern; nAMD, neovascular age-related macular degeneration; PRN, pro re nata regimen; T+E, "treat-and-extend" regimen.

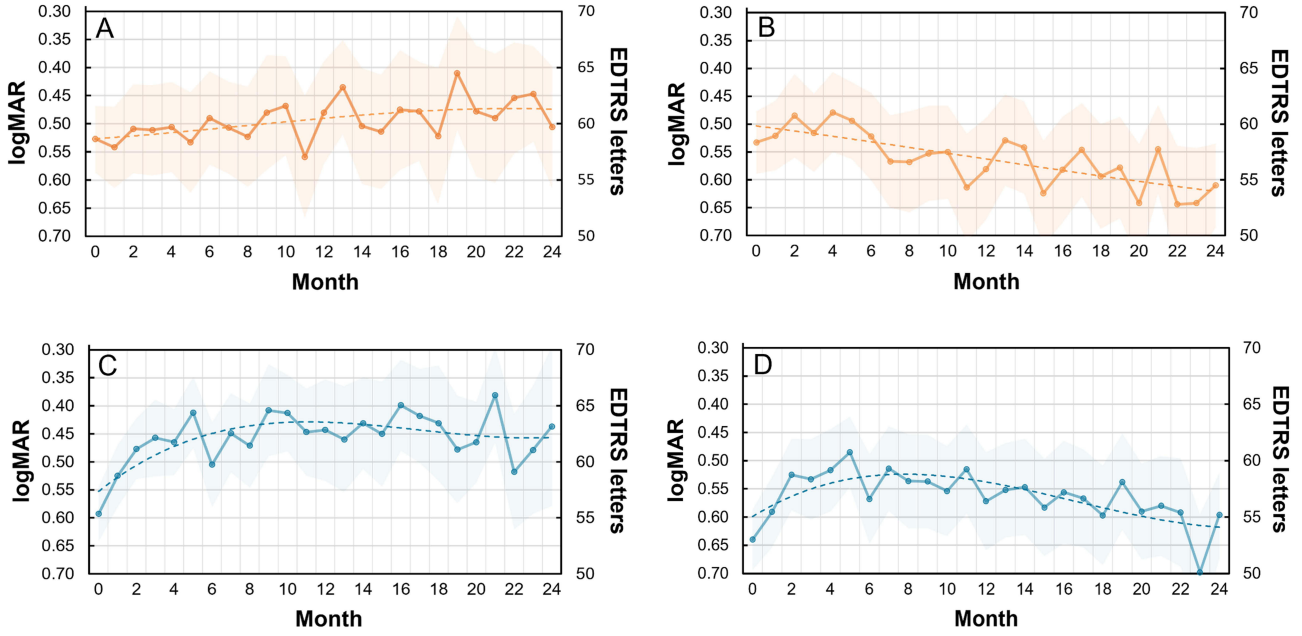

Figure 2 BCVA in logMAR and ETDRS letters, for pre-treated patients with treatment regimen "treat and extend" (**A**), all pre-treated patients (**B**), treatment-naïve patients with treatment regimen "treat and extend" (**C**), and all treatment-naïve patients (**D**) (FAS). Figures show mean values (data points) with 95% confidence intervals (transparent band).
Abbreviations: BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; FAS, full analysis set; logMAR, logarithm of the minimum angle of resolution.

treatment-naïve patients (n=162 patients at baseline, n=25 patients at month 24; Figure 2C). In EDTRS letters, the BCVA for patients treated according to a strict "treat-and-extend" regimen increased from 58.6 at baseline to 59.7 at month 24 for the pre-treated patients and from 55.3 at baseline to 63.2 at month 24 for the treatment-naïve patients.

For the overall population of pre-treated patients, visual acuity decreased continuously (n=1405 patients at baseline, n=263 patients at month 24; Figure 2B) and for the overall population of treatment-naïve patients, visual acuity decreased after month 5 until month 24 (n=1564 patients at baseline, n=283 patients at month 24; Figure 2D). In EDTRS letters, the BCVA for the overall population of patients decreased from 58.3 at baseline to 54.5 at month 24 for the pre-treated patients, while it changed from 53.0 at baseline to 60.8 at month 5 to 55.2 at month 24 for the treatment-naïve patients.

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Additional comparative data are provided in the supplementary materials, showing BCVA and CRT values at baseline, after month 3, and at the end of the observation period for patients treated with observe and extend and treat and extend regimens. These tables enable direct evaluation of both anatomical and functional outcomes by the dominant treatment pattern (see Supplementary Tables 1–3).

Discussion

Intravitreal anti-VEGF has become the gold standard for the treatment of nAMD. However, significant barriers are associated with this intervention and the corresponding regimen. A treatment regimen that can be easily implemented by both clinician and patient is of fundamental importance to achieve optimal clinical outcomes.[24] In the non-interventional PACIFIC study, the functional and morphological success of the applied treatment regimens was documented in almost 5000 patients in different approved indications for anti-VEGF therapy with ranibizumab.

Of the 3051 patients with nAMD, 1461 patients (47.9%) were pre-treated and 1590 patients (52.1%) were treatment-naïve. The overall most common actually performed treatment regimen corresponded to a watchful waiting pattern (ie, follow-up visits without injection; pre-treated: 70.4%; treatment-naïve patients: 68.6%). This showed a clear discrepancy to the originally planned treatment pattern. At baseline, *pro re nata* and a fixed regimen were the most commonly planned treatment regimens in both treatment groups. For both, pre-treated as well as treatment-naïve patients, more than 90% received the baseline injection only in the study eye, with around 5 injections over the course of the first study year. The number of injections over the entire 24-month observational period was about 7 injections for both pre-treated and treatment-naïve patients. There was overall no remarkable difference for the number of injections between both patient groups according to the different treatment regimes, with the notable exception of patients treated with the "treat-and-extend" regime. Pre-treated and naïve patients treated with this regimen received a similar amount of injections on average over the whole observational period (12.34 and 11.84, respectively). With respect to the treatment of nAMD patients, the "treat-and-extend" regimen emerged as highly effective with visual acuity constantly increasing for both pre-treated and treatment-naïve patients. Particularly for treatment-naïve patients, a sustained benefit was observed. Functional and morphological examinations were more frequent in treatment-naïve patients. The results of this 2-year observational study show that treatment-naïve nAMD patients with a "treat-and-extend" regimen have a low risk of being undertreated. The essential diagnostic tools OCT and FLA should be used more frequently for the initial diagnosis of nAMD.[2] Treatment of both eyes on the same day was performed more often in pre-treated patients. Mean treatment delay from study start visit to first injection was approximately 11 days for pre-treated and 9 days for treatment-naïve patients. This is significantly shorter than in the real-life OCEAN study, which was performed between 2011 and 2016 and reported a mean treatment delay for nAMD patients of about 20 days.[25,26] This shows that ophthalmologists were aware of the benefits and need of an early treatment start and try to overcome treatment delays.

In addition to functional outcomes, morphological changes were assessed based on central retinal thickness (CRT) measurements over the observational period. Supplementary data showed that CRT decreased in both the "treat-and-extend" (T+E) group and the "observe-and-extend" pattern from baseline to month 3 and remained relatively stable through month 24. These findings support a sustained anatomical response under continuous anti-VEGF therapy, particularly in the "treat-and-extend" group, where CRT remained below baseline values at all timepoints. Visual acuity (BCVA) also improved or stabilized more clearly in the "treat-and-extend" group across both pre-treated and treatment-naïve patients. In contrast, patients experienced a decline in BCVA after the observational approach by month 24—despite an initial short-term improvement, suggesting a potential risk of undertreatment or reactivation-related vision loss in this group. These data further support current clinical preference for proactive, individualized regimens like "treat-and-extend". The classification of patients into treatment regimens was based on documented injection intervals and visit timing rather than on protocol intent.

Thus, patients may have been statistically assigned to the "observe-and-extend" pattern due to delays or irregularities in visit schedules, even if initially treated under a "treat-and-extend" rationale. Additionally, re-injections should reflect the need to respond dynamically to disease activity—even within an observational framework. A formal switch of regimens was not documented in the study database, but practical transitions between intended and applied strategies likely occurred and are inherent to routine clinical management. Median injection numbers provided in Supplementary Table 1 further highlight the differences in treatment intensity between regimens, with higher injection frequency observed in "treat-and-extend" groups—consistent with their superior visual outcomes.

Due to the non-interventional and observational nature of the PACIFIC study, no formal hypothesis testing was performed, and p-values were not reported. Instead, descriptive statistics and confidence intervals were provided to illustrate data variability and the precision of estimates. This approach reflects current best practices for real-world evidence studies, where randomization and control of confounding variables are not feasible, and inferential testing may be inappropriate or misleading.

Real-world data help to develop and improve real-world treatment strategies, eg, in nAMD, with the aim of optimizing visual outcomes and reducing treatment burden in clinical practice.[22] Daien et al have done a literature search on studies conducted to investigate the real-world effectiveness of anti-VEGF treatment regimens for nAMD. The authors examined the status of the different treatment regimens (*pro re nata*, fixed regimen, "treat-and-extend") and their impact on the care of nAMD patients. They showed that in everyday practice, a "treat-and-extend" regimen has the most potential to ensure a balance between therapy effectiveness and patients' treatment barriers, with fewer hospital visits compared to fixed or *pro re nata* dosing.[22] Therefore, the "treat-and-extend" regimen is becoming more accepted in all indications.

Similarly, Ziemssen et al have developed a model to quantify the influence of variables such as treatment delay and undertreatment on the success of anti-VEGF therapy. The authors concluded that frequent monitoring and injections are essential for improvement of visual acuity.[17]

In the PACIFIC study, the initially planned treatment regimens and the last regimens actually performed for each patient were observed. Over the course of the observational period, a majority shift toward an observational approach was observed, based on the assignment of the actual treatment data. It may be due to the defined temporal limits that the data was interpreted as an approach like "observe-and-extend" in many cases, even if this was not the physician's intended regimen. Differences in treatment response could also be attributed to the heterogeneous patient population with the presence of various comorbidities, many of which are excluded from prospective clinical trials. Additionally, recent insights into the fluid dynamics and leakage pathways in AMD further underscore the complexity of differentiating between exudative and non-exudative fluid, which is critical when considering an observe and extend approach.[19,27]

The inclusion of both pre-treated and treatment-naïve patients introduced heterogeneity, thereby limiting direct comparisons of treatment efficacy across regimens. Treatment-naïve patients generally provide a more homogenous baseline, and thus a more suitable group for comparative outcome analyses. Although a stratified statistical analysis limited to treatment-naïve patients was considered, the real-world nature of the data—with greatly differing group sizes, variable follow-up durations and adherence—precluded meaningful statistical comparisons across all regimens. Future studies with a more uniform treatment history and standardized follow-up schedules are warranted to definitively assess regimen-specific outcomes.

A major strength of the PACIFIC study is its large, multicenter design encompassing a broad patient population reflective of routine clinical practice in three countries. The inclusion of both pre-treated and treatment-naïve patients offers a comprehensive perspective on treatment strategies across different clinical contexts. Additionally, the prospective and observational nature of the study allows for the capture of real-world behaviors, including treatment adherence and variability in practice patterns. However, certain limitations must be acknowledged. The lack of a standardized treatment protocol contributed to the heterogeneity in treatment intensity and activity assessment, potentially affecting the comparability of outcomes across groups. Most notably, the assignment may have misrepresented some "treat-and-extend" cases to the observational approach, due to deviations in injection timing beyond the defined ±7-day window. This classification error could have contributed to the unexpectedly high prevalence of the "observe-and-extend" pattern, which—by strict clinical definition—should only be used in select cases of disease inactivity or suspicion of non-neovascular fluid. Furthermore, the limited documentation or underuse of imaging modalities such as OCT and FLA may have impacted the accuracy of disease activity assessment and treatment decision-making. These limitations underscore the need for improved regimen tracking and documentation, as well as clearer differentiation between similar-sounding treatment strategies. Future studies should consider incorporating stricter criteria or physician-confirmed intent for regimen classification to enhance interpretability and relevance to clinical guidelines.

Conclusions

The PACIFIC study provides insights into the real-world application of anti-VEGF treatment in nAMD. While the "observe-and-extend" pattern was the most commonly documented approach, this finding must be interpreted cautiously. The distinction from "treat-and-extend" with delayed re-treatment is difficult, when just looking at the control visits and injection data. From a clinical perspective, the data underscore the likely advantages of a more consistent "treat-and-extend" on visual outcomes, especially for treatment-naïve patients. The study highlights the importance of maintaining treatment intensity and monitoring rigorously to avoid undertreatment—common pitfalls in real-world settings. The findings supported ongoing efforts to standardize regimen definitions and encourage adherence to evidence-based practices, ultimately aiming to optimize visual prognosis while reducing the treatment burden.

Abbreviations

AE, Adverse event; AMD, Age-related macular degeneration; BCVA, Best-corrected visual acuity; BMI, Body Mass Index; ETDRS, Early treatment diabetic retinopathy study; FAS, Full analysis set; FIX, Fixed regimen; FLA, Fluorescence angiography; logMAR, Logarithm of the minimum angle of resolution; MedDRA, Medical Dictionary for Regulatory Activities; nAMD, Neovascular age-related macular degeneration; O+E, Observe and extend regimen; OCT, Optical coherence tomography; PRN, Pro re nata regimen; SD, Standard deviation; SES, Safety evaluation set; T+E, Treat and extend regimen; VEGF, Vascular Endothelial Growth Factor.

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