# Long-Term Real-World Outcomes of Anti-VEGF Treatment in Early Good Responders with Neovascular Age-Related Macular Degeneration

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## ABSTRACT

**Objective:** To evaluate long-term visual and anatomical outcomes in eyes with neovascular age-related macular degeneration (nAMD) that responded favorably to initial anti-VEGF loading therapy.

**Materials and Methods:** This retrospective study included 55 eyes of 55 patients with at least 12 months of follow-up. Early good responders (EGR) were defined as those who showed ≥5 letter gain in BCVA, complete resolution of intraretinal/subretinal fluid, reduction in lesion size, and disappearance of subretinal hemorrhage after three loading injections. Retreatments were guided by visual decline, fluid on OCT, or persistent/new hemorrhage.

**Results:** The mean baseline BCVA improved from 51.1 ± 22.6 letters to 63.9 ± 21.5 after loading and was 58.5 ± 23.1 at the end of year-5 ($p<0.001$ and $p=0.003$ vs. baseline). Although BCVA decreased between month 3 and year 1 ($p=0.009$), it remained stable thereafter. Central foveal thickness decreased significantly from 327.9 ± 166.9 µm to 195.3 ± 97.1 µm post-loading and to 175.7 ± 59.6 µm at final visit ($p<0.001$). The mean annual number of injections declined from 5.1 in year 1 to 2.4 in year 5. Visual decline after loading was seen in 51% of eyes, mostly due to lesion activity (57%) or atrophy (43%). Notably, 27.2% of eyes required no further injections after the loading phase during the first year. No cases of tachyphylaxis or treatment switch were observed.

**Conclusions:** EGR patients with nAMD can sustain functional and anatomical improvements over 5 years with significantly fewer injections. A substantial subset may require minimal or no additional treatment following initial therapy.


**Keywords:** Age-related macular degeneration, neovascular AMD, Anti-VEGF, early good responders, long-term results

## INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness among patients over 55.[1] The neovascular form of AMD (nAMD), in particular, is the primary cause of visual acuity impairment.[2] Intravitreal Anti-VEGF (Anti-vascular endothelial growth factor) injections have been the mainstay of treatment of nAMD for the last two decades.[3,4] The effectiveness of this therapy is typically assessed through changes in best-corrected visual acuity (BCVA) and optical coherence tomography (OCT).[5] Although anti-VEGF therapy is generally effective for treating nAMD, suboptimal responses can still occur.[6] The responses of nAMD patients to anti-VEGF therapy can be classified as good, partial, poor, or non-responsive based on anatomical and functional outcomes.[7] Early response is

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best determined at the end of the loading period (after the third injection), while late response is assessed at any time following the loading period.[8] It is possible for the same patient to exhibit different responses during the early and late phases of treatment.[9] Some patients had early good responses to anti-VEGF treatment that converted to poor or no response afterward. This change may result from tachyphylaxis, tolerance, treatment-related complications, or the patient's noncompliance with the treatment regimen.[8,10]

The response to anti-VEGF therapy is influenced by various factors, including the patient's age, lesion characteristics, lesion duration, baseline visual acuity, and specific genotype risk alleles.[11–13] The variability in patient response to anti-VEGF therapy highlights the importance of distinguishing subgroups such as early good responders (EGR) to optimize long-term management strategies. While a good response to initial intravitreal anti-VEGF treatment is a well-defined condition, data on the long-term outcomes of these early good responders (EGR) remains limited. In this study, we aimed to evaluate the long-term outcomes of patients with an early good response recruited from our previous study.[13] Understanding the natural course of treatment-responsive patients is critical for optimizing long-term management strategies and resource allocation in real-world settings.

## MATERIALS AND METHODS

In a previous study conducted by two authors of the present paper, the prevalence of single nucleotide polymorphisms in complement factor H and VEGF in nAMD and their relationship with the response to intravitreal anti-VEGF treatment were evaluated.[13] In that study, patients were divided into early good responders (EGR) and non-responders. The EGR group was defined as patients who exhibited a reduction in activity score, a gain of at least five letters in BCVA, total resolution of intraretinal or subretinal fluid, a decrease in lesion size, and disappearance of subretinal hemorrhage after anti-VEGF treatment.[13] The records of EGR patients from that study were reviewed for inclusion in the current study. Only patients with at least 12 months of regular follow-up were included. The number of patients, visits, and injections was recorded at baseline, month 3, and annually thereafter. Ethical approval for the study was obtained from the Gazi University Clinical Research Ethics Committee in adherence to the Declaration of Helsinki.

All medical records were reevaluated retrospectively to analyze the long-term outcomes of the EGR group in a real-world setting. At the initial examination, BCVA, a complete ophthalmological evaluation, OCT, and fluorescein angiography (FA) were performed on all eyes. BCVA using ETDRS letters, slit lamp examination findings, and OCT results were documented at each visit. Fundus auto-

fluorescence and SD-OCT were assessed to evaluate retinal pigment epithelium (RPE) atrophy, and FA was used to confirm lesion activation. Data on the number of injections, treatment regimens, follow-up duration, and visual and anatomical responses (determined by OCT) were collected. Comparisons were made between baseline, post-loading phase, yearly, and final follow-up visual acuities and central foveal thickness (CFT) measurements from OCT. The total number of visits and injections per year were recorded. Additionally, the number of eyes that required no further treatment during the follow-up period was identified.

Patients were followed on a monthly pro re nata (PRN) basis. The criteria for reinjection included decreased visual acuity, the presence of fluid on OCT, new or persistent hemorrhage, and leakage observed on FA.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.). The Wilcoxon signed-rank test was used to compare two related samples.

## RESULTS

The data of 62 eyes of 62 EGR patients who received Anti-VEGF treatment between 2007 and 2024 in the previous retrospective study[13] were reviewed. Seven eyes (11.2%) were excluded due to missing data or irregular follow-up. The final cohort consisted of 55 eyes from 55 patients (22 female, 33 male), with a mean age of 71 ± 8 years (range: 55–90). The mean follow-up was 42.7 ± 25 months (min: 12 months). Ranibizumab was administered to 83.7% of eyes, while 16.3% received bevacizumab.

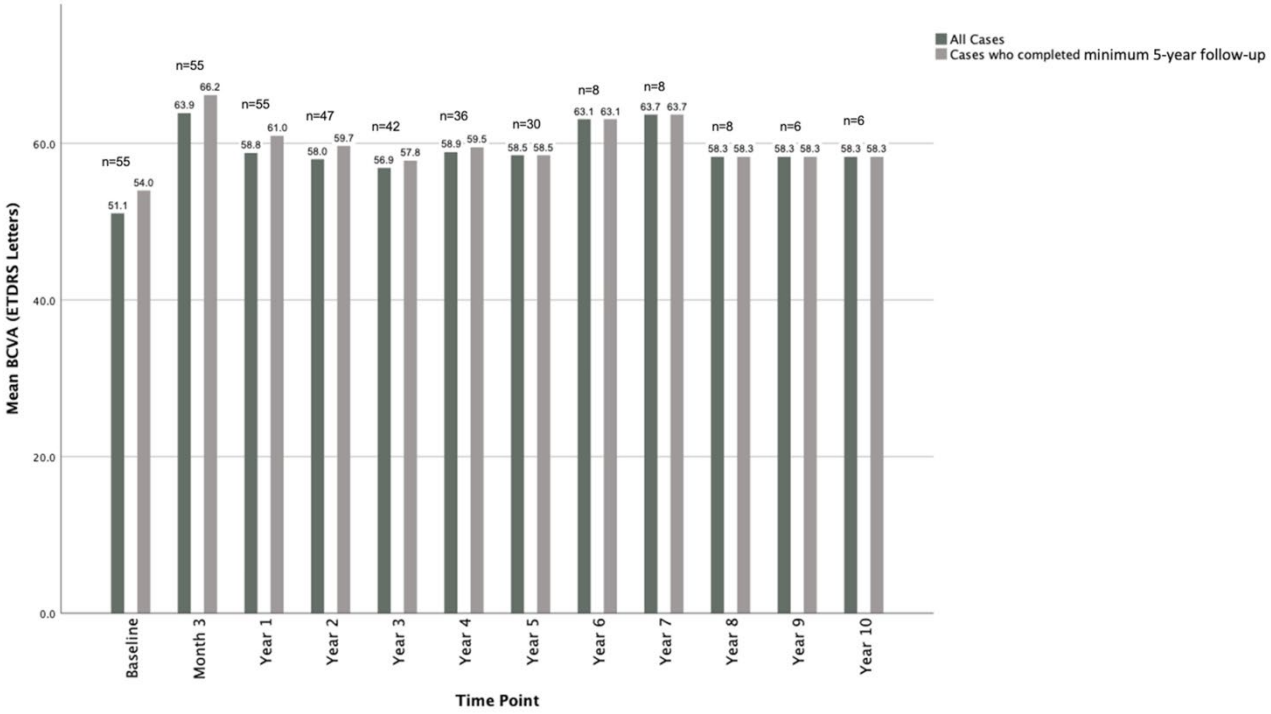


**Figure 1.** *Mean best-corrected visual acuity with ETDRS letters of all patients and patients who completed minimum 5-year follow-up.*

**Table 1.** *Best-corrected visual acuity and central foveal thickness measurements of patients during follow-up.*

| | Baseline | Month 3 | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|---|
| Patient number (%) | 55 (100) | 55 (100) | 55 (100) | 47 (85.4) | 42 (76.3) | 36 (65.4) | 30 (54.5) |
| BCVA±SD (ETDRS letters) | 51.1±22.6 | 63.9±21.5 | 58.8±22.9 | 58±23.3 | 56.9±22.6 | 58.9±22 | 58.5±23.1 |
| Range (ETDRS letters) | 5 – 80 | 5 – 85 | 10 – 85 | 10 – 85 | 10 – 85 | 10 – 85 | 10 – 85 |
| P value (for BCVA) | | <0.001* | 0.003*/ 0.009** | 0.139*/ 0.04** | 0.207*/ 0.05** | 0.086*/ 0.027** | 0.214*/ 0.017** |
| CFT±SD (µm) | 327.8 ± 166.9 | 195.3 ± 97.1 | 221.9±90.1 | 214±86.7 | 194±69.1 | 174.8±69.3 | 175.7±59.6 |
| Range (µm) | 88 – 1000 | 90 – 500 | 36 – 593 | 35 – 501 | 35 – 345 | 33 – 310 | 52 – 288 |
| p value | | <0.001# | <0.001#/ 0.001## | <0.001#/ 0.007## | <0.001#/ 0.27## | <0.001#/ 0.49## | <0.001#/ 0.59## |

*Statistical difference when compared to baseline BCVA, ** Statistical difference when compared to month 3 BCVA, # Statistical difference when compared to baseline CFT, ## Statistical difference when compared to month 3 CFT, BCVA: Best-corrected visual acuity; SD: standard deviation; ETDRS: early treatment for diabetic retinopathy study; CFT: central foveal thickness.

*Visual Acuity Outcomes*

The mean baseline BCVA was 51.1 ± 22.6 letters (range: 5–80), which improved to 63.9 ± 21.5 letters after loading and declined slightly to 58.5 ± 23.1 letters at the end of year 5 **(Figure 1)**. Statistically significant gains were observed at month 3 and year 1 ($p < 0.001$ and $p = 0.003$; respectively). However, BCVA at year 1 was significantly lower than month 3 ($p = 0.009$). No significant differences were observed between years 1–5 or between baseline and years 2–5 ($p > 0.05$). At final visit, 28 eyes (51%) had lower BCVA than post-loading, due to recurrent activity (57%) or RPE atrophy (43%).

In the 30 patients completing 5-year follow-up, mean BCVA improved from 54.0 ± 21.8 to 66.2 ± 20.1 after loading, and was 58.5 ± 23.1 letters at year 5. Significant gains were seen at month 3 and year 1 ($p < 0.001$ and $p = 0.048$) **(Table 1)**. There were no significant differences in BCVA from year 1 to year 5 ($p>0.05$).

Among all patients, 52.7% maintained post-loading BCVA after 1 year, and 46.6% of those with 5-year data preserved post-loading gains. Furthermore, 66.6% of these retained year 1 BCVA through year 5.

*Central Foveal Thickness*

Baseline CFT was 327.9 ± 166.9 µm, reducing to 195.3 ± 97.1 µm after loading and 175.7 ± 59.6 µm at the end of year 5 **(Figure 2)**. All reductions from baseline were significant ($p < 0.001$). Compared to post-loading measurements, CFT showed a significant increase at year 1 ($p = 0.001$) and year 2 ($p = 0.007$), which normalized in the following years ($p > 0.05$ for years 3, 4, and 5). **(Table 1)**.

In patients with 5-year data, mean CFT declined from 322.6 ± 178.7 µm to 195.3 ± 95.5 µm post-loading and 175.7 ± 59.6 µm at year 5. These reductions were significant at all time points vs. baseline ($p < 0.01$).

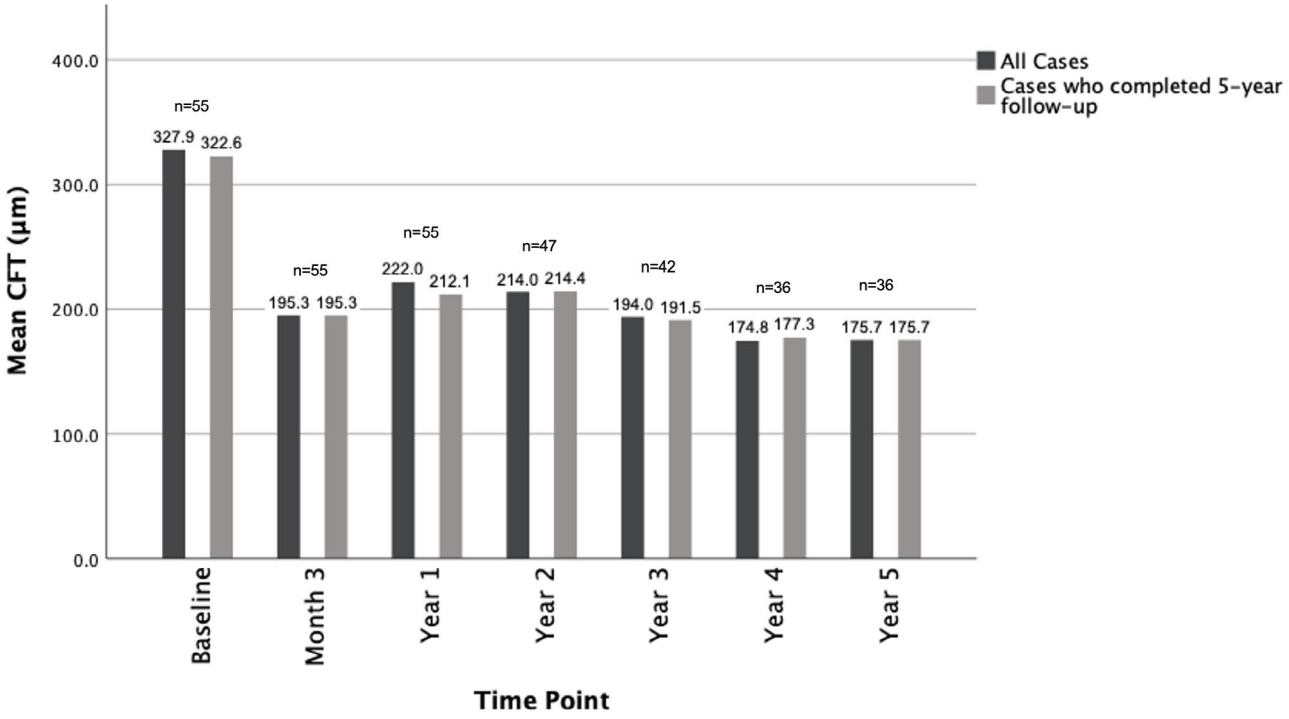


**Figure 2.** *Mean central foveal thickness measured with optical coherence tomography of all patients and patients who completed 5-year follow-up.*

**Table 2.** *Number of patients without reactivation of the disease, visits and injections during 5-year follow-up*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Patients n (%) | 55 (100) | 47 (85.4) | 42 (76.3) | 36 (65.4) | 30 (54.5) |
| Eyes without reactivation n (%) | 15 (27.2) | 15 (31.9) | 12 (28.6) | 11 (30.5) | 13 (43.3) |
| Mean number of visits | 8.0 | 7.1 | 6.7 | 6.8 | 5.5 |
| Mean number of injections ± SD (Range) | 5.1±2.0 (3-12) | 2.6±2.4 (0-9) | 2.6±2.5 (0-9) | 2.6±2.3 (1-9) | 2.4±2.2 (0-8) |
| p value* | | <0.01 | <0.01 | 0.02 | <0.01 |

*Statistical difference in the number of injections compared to the first year
SD: Standard deviation

*Treatment Intensity and Compliance*

The mean number of visits in year 1 was 8.0, with decreasing trends in subsequent years. Injections averaged 5.1 ± 2.0 in year 1 and 2.4 ± 2.2 by year 5 ($p < 0.001$). No significant differences were found between years 2–5 ($p > 0.05$) **(Table 2)**.

Mean total injection count was 12.3 ± 9.1 (range: 3–38) for the full cohort, and 16.4 ± 9.7 (range: 3–30) in those completing 5 years. Fifteen eyes (27.2%) required no further injections after the loading dose during the first year, and two eyes (3.6%) required no injections for the entire 60-month follow-up period (Table 2). At final visit, 10 of 30 eyes (33.3%) had active choroidal neovascular (CNV) and were still under treatment.

*Correlation Analysis*

There was no correlation between injection count and lesion type or baseline CFT ($R = –0.09$ and $–0.16$; $p = 0.5$ and 0.2). However, a significant negative correlation was observed between baseline BCVA (LogMAR) and injection number ($R = –0.39$; $p = 0.007$), indicating that better initial acuity predicted more intensive treatment.

*Extended Follow-up (Beyond 5 Years)*

Seventeen patients had data beyond 5 years, but only 8 maintained uninterrupted follow-up (Figure 1). Six patients were monitored through year 10. Mean BCVA at years 6–10 were: 63.1, 63.75, 58.33, 58.33, and 58.33 letters, respectively. Injection counts were 4.62, 2.25, 2.0, 1.5, and 3.0 annually. Due to inconsistent follow-up, data beyond 5 years were excluded from primary analysis.

*Safety & Other Observations*

No cases of tachyphylaxis or anti-VEGF switching were observed. No serious ocular complications occurred (e.g., endophthalmitis, glaucoma, retinal detachment, etc.).

## DISCUSSION

The present study demonstrated that the anatomical outcomes achieved with loading injections in EGR patients were preserved over the five-year follow-up period. Regarding long-term functional outcomes, although the visual acuity gained after the loading dose declined over time, there was no reduction in BCVA at the final visit compared to baseline. During follow-up, the number of visits and injections decreased and 27% of patients required no additional treatment after the initial loading dose during the first year.

The early treatment response criteria we used—complete resolution of intraretinal/subretinal fluid, reduced lesion size, and disappearance of hemorrhage—were more stringent than Amoaku et al.'s morphologic criteria based on OCT metrics alone.[7] In EGR patients treated with PRN anti-VEGF therapy, the mean BCVA gain was 12.8 letters at month 3, 7.8 letters at year 1, and 7.4 letters at year 5.

Long-term outcomes of anti-VEGF therapy in nAMD have been extensively evaluated through extensions of randomized controlled trials (RCTs), most of which shifted to a pro re nata (PRN) protocol, as well as in several real-world retrospective studies. The seven-year follow-up data from the ANCHOR, MARINA, and HORIZON trials—each employing the PRN regimen—revealed a mean BCVA decline of 8.6 letters from baseline to the end of the study.[14] Similarly, the five-year results of the CATT trial reported a mean BCVA change of -3 letters from baseline and -11 letters compared to year 2.[15] In contrast, Adrean et al. reported a mean BCVA gain of 8.7 letters after an average of 50 anti-VEGF injections over eight years in patients managed with a treat-and-extend protocol.[16] Cheema et al., presenting ten-year real-world data, observed an average BCVA loss of 11.2 letters.[17] Ozkaya et al. documented that after five years of ranibizumab therapy, 45.5% of patients main-

tained or improved vision, whereas 54.5% experienced vision loss of three or more lines compared to baseline.[18]

Prognostic indicators have also been identified: Nguyen et al.[19] found that visual acuity at the fourth injection strongly predicts year-3 outcomes, and Chae et al.[20] suggested that vision at three months is the most reliable predictor of long-term success. Despite these valuable findings, most prior studies did not account for differential treatment responsiveness, such as early good responders (EGRs), thus limiting insight into this specific subgroup.

Our study directly addresses this gap by focusing solely on EGR patients. We found that while some loss in BCVA occurred after the initial gain post-loading dose, the BCVA achieved at year 1 was sustained through year 5. Notably, the mean long-term BCVA gain was 7.4 letters, suggesting that early response may predict long-term functional benefit. This highlights the prognostic importance of early treatment response and underscores the potential for individualized follow-up strategies based on early outcomes.

Treatment responsiveness in nAMD is known to be multifactorial. Genetic polymorphisms and abnormalities in the complement system have been implicated in influencing therapy outcomes.[21–23] Interestingly, some patients classified as poor responders in the short term may exhibit delayed improvement, while some EGR eyes may show transition to be suboptimal responders over time due to tachyphylaxis or tolerance.[10,24] The reported incidence of tachyphylaxis ranges from 2% to 10%.[8,10] In a large 12-year cohort study involving 7,802 patients, 1,923 required a switch in therapy due to inadequate response.[25] In contrast, none of the patients in our EGR cohort required a treatment switch, nor were there any cases of tachyphylaxis or tolerance, suggesting that EGR status may represent a biologically distinct subgroup with sustained responsiveness to anti-VEGF therapy.

In real-world practice, four main treatment strategies are employed for nAMD: fixed monthly dosing, pro re nata (PRN), treat-and-extend, and individualized fixed regimens. In our cohort, the initial loading phase—three anti-VEGF injections—was sufficient to control disease activity for one year in 27.2% of eyes, with no additional injections required. This outcome supports the PRN approach as a suitable strategy for managing early good responders (EGR), minimizing overtreatment. Similarly, Kuroda et al. observed that 25.2% of their patients had no disease recurrence over a 24-month period.[26]

Our findings also align with prior studies reporting that patients with better baseline visual acuity tend to require more injections during follow-up. Lovestam Adrian et al.[27] noted that individuals with baseline BCVA ≥70 letters received a greater number of injections, and baseline visual acuity has been widely recognized as a strong predictor of treatment demand in AMD.[20] However, due to the ceiling effect, patients with high initial visual acuity may show limited functional gain, making anatomical response the more prominent treatment marker in this subgroup.

Thomsen et al. recently emphasized that early anatomical and visual responses post-loading are predictive of one-year outcomes, with good initial responders being more likely to sustain both functional and morphological stability.[28] Therefore, although functional gains may plateau in patients with better baseline vision, maintaining anatomi-

cal integrity in such eyes might necessitate higher injection frequencies.

While choroidal neovascular activity tends to diminish over time with anti-VEGF treatment, this does not always translate into sustained functional improvement.[14,15,29] The CATT and SEVEN-UP trials both highlighted retinal pigment epithelium atrophy as a major contributor to long-term vision loss, independent of CNV activity. In these studies, approximately one-third of patients experienced poor visual outcomes primarily due to RPE atrophy rather than ongoing neovascularization.[14,15] Consistent with these findings, our study showed that visual acuity declined below baseline levels in nearly half of the eyes by the final visit. Among these, persistent fluid accounted for 57% of the vision loss cases, while atrophy was responsible in the remaining 43%. This suggests that long-term RPE atrophy is a prominent concern in EGR patients, even for those who initially respond well to anti-VEGF therapy.

Long-term adherence to anti-VEGF therapy remains a significant challenge in nAMD management. Consistent with previous studies, our findings revealed that more than half of patients were lost to follow-up by the end of five years.[30,31] Factors contributing to poor adherence include financial limitations, physical disability, perceived lack of disease activity, fear of injections, suboptimal treatment response, and mortality.[30,32,33]

The COVID-19 pandemic has emerged as a major disruptor of treatment continuity. Montesel et al. reported that, among 147 patients who postponed intravitreal therapy during lockdown, 35 were lost to follow-up or had incomplete data, illustrating the pandemic's adverse impact on adherence and data integrity.[34] Similarly, in our cohort, follow-up became increasingly irregular after the onset of the pandemic. To avoid bias introduced by declining cohort size and inconsistent visits, post-pandemic data were excluded from the primary analysis. Interestingly, in a subgroup of eight patients who maintained consistent follow-up beyond five years, BCVA gains were largely preserved, even with a reduced injection frequency of only 2–3 injections annually. This suggests that, in selected EGR patients, long-term functional stability may be achievable with less intensive treatment—though validation in larger prospective cohorts is warranted.

The primary limitations of this study are its retrospective design and relatively small sample size. While numerous long-term studies have assessed anti-VEGF therapy in nAMD, none have focused specifically on early good responders in a real-world setting. To our knowledge, this is the first study to independently evaluate long-term outcomes in EGR patients, outside the context of multicenter trials.[14,15,35] Future prospective studies with larger cohorts and extended follow-up periods are warranted to further characterize this subgroup.

In conclusion, EGR patients appear capable of maintaining favorable anatomical outcomes and stable BCVA gains with fewer injections over a five-year period. Notably, in over one-quarter of cases, the initial three loading injections were sufficient to control disease activity during the first year. Among these patients, RPE atrophy emerged as the leading cause of long-term visual decline, while tachyphylaxis or treatment tolerance was not observed. These findings support the potential of personalized, less intensive treatment strategies for selected EGR patients in clinical practice.

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