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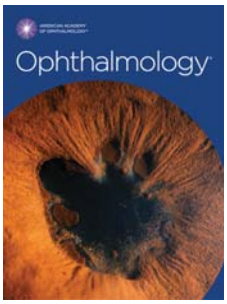

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Projection of long-term visual acuity outcomes based on initial treatment response in neovascular age-related macular degeneration

Vuong Nguyen PhD[1], Vincent Daien MD PhD[1,2,3], Robyn Guymer MBBS PhD[4], Stephanie Young MBBS[5], Alex Hunyor MBBS[1,6,7], Samantha Fraser-Bell MBBS PhD[1,6,7], Adrian Hunt MBBS[8], Mark C Gillies MBBS PhD[1,7] and Daniel Barthelmes MD PhD[1,9]; the Fight Retinal Blindness! Study Group

[1]The Save Sight Institute, Sydney Medical School, The University of Sydney, Sydney, NSW
[2]Department of Ophthalmology, Gui De Chauliac Hospital, Montpellier, F-34000, France
[3]Inserm, U1061, Montpellier, F-34093, France
[4]Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Australia
[5]Gladesville Retina, NSW, Australia
[6]Retina Associates, Chatswood, NSW, Australia
[7]Sydney Eye Hospital, NSW, Australia
[8]Department of Ophthalmology, Westmead Hospital, NSW, Australia
[9]Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

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Corresponding Author: Vuong Nguyen, 8 Macquarie Street, The Save Sight Institute, Sydney Medical School, The University of Sydney, Sydney, 2000, NSW, Australia. Email: phuc.nguyen@sydney.edu.au

Abstract

Purpose: To explore various methods for assessing the early response to vascular endothelial growth factor (VEGF) inhibitors for neovascular age-related macular degeneration and investigate their association with 3 year visual acuity (VA) outcomes.

Design: Observational study from a prospectively collected registry.

Participants: Treatment-naïve eyes in the Fight Retinal Blindness! outcomes registry that commenced anti-VEGF therapy between 1st January 2007 and 1st March 2014 that received 3 anti-VEGF injections within the first 3 months.

Methods: The early response was defined as occurring up until the 4th injection. Various early response metrics, which included both continuous and categorical variables, were explored: 1) achieving good VA (≥70 letters [20/40]), 2) absolute change in VA from baseline, 3) time to first grading of the choroidal neovascular lesion as inactive, 4) maximum rate of VA change between successive injections.

Main Outcome Measures: Proportion of eyes achieving ≥70 letters at 3 years.

Results: This study included 2051 treatment-naïve eyes from 1828 patients. Achieving good vision at 3 years was significantly associated with 1) having good vision by the 4th injection (odds ratio [95% CI]: 9.8 [6.5, 14.7] for VA≥70 vs. VA<70 letters), 2) small (1-5 letters) or large (>5 letters) early VA gains (1.8 [1.2, 2.6], P = 0.002 and 1.8 [1.3, 2.5], P < 0.001 vs. eyes with early VA loss), 3) fewer injections until first grading of lesion inactivity (1.6 [1.2, 2.1], P < 0.001 for ≤3 vs. >3 injections), 4) gradual change (between -4 and 4 letters) or rapid (>5 letters) gains between successive injections (1.7 [1.1, 2.6], P = 0.015 and 1.6 [1.1, 2.3], P = 0.018 for gradual change and rapid gain vs. rapid loss). Eyes that achieved small or large early gains achieved similar vision at 3 years (65.0 and 64.7 letters respectively), and had better vision than eyes with early VA loss (57.2 letters).

Conclusions: Attainment of good vision by the 4th injection was strongly associated with 3 year visual outcomes, while other early response parameters had a moderate association. The early response during the initial 3 monthly loading doses can be a useful guide for subsequent treatment decisions.

Introduction

Large variations in the response to vascular endothelial growth factor (VEGF) inhibitors in patients with neovascular age-related macular degeneration (nAMD), as reported in clinical and observational studies, have been attributed to a number of factors, notably demographic and clinical characteristics at baseline and treatment protocols.[1-7] Baseline clinical characteristics such as age, lesion size and lesion subtype in particular have been identified in multiple studies as predictive of visual outcomes. [1, 2, 8, 9] In addition, several studies have assessed the effect of genetic factors on treatment outcomes, but these associations are weaker or non-existent.[4, 10-12] By contrast, the visual acuity (VA) at presentation is one of the strongest predictors of long-term outcomes, whereby eyes with poor starting VA are more likely to achieve larger gains in vision, but have worse final vision than those that present with good VA.[4, 5, 8]

While VEGF inhibitors have generally been shown to provide good visual outcomes for nAMD, some eyes do not respond well to treatment.[5] Predictive markers based on an eye's early response to treatment may assist in making subsequent treatment decisions and guiding patient expectations. A post-hoc analysis of the Comparison of AMD Treatments (CATT) cohort identified the 12 week change in VA to provide significantly more predictive power for 2 year outcomes compared with the baseline and 4 week response. [13] In the present study, we explored various metrics for measuring the early response to treatment with VEGF inhibitors, and assessed their ability to predict 3 year visual outcomes. We also assessed whether these early response markers provided additional predictive power that could not already be inferred from the baseline vision.

Methods

This study followed the STROBE checklist items for reporting observational study data. [14]

Study Design

Observational study using data from a prospectively collected registry.

Setting

Data were obtained from the Fight Retinal Blindness! (FRB!) database, a large international registry that tracks real-world outcomes of treatment of nAMD. The FRB! database is compliant with the International Consortium for Healthcare Outcome Measurement's (ICHOM) minimum standard set of treatment outcomes for macular degeneration.[15] Further details of the FRB! database have been published elsewhere.[16] Ethics approval was obtained from the Human Research Ethics Committees of the Royal Victorian Eye and Ear Hospital, the Royal Australian and New Zealand College of Ophthalmologists, the University of Sydney and the Cantonal Ethics Committee Zurich, Switzerland. This study conformed to the tenets of the Declaration of Helsinki.

Data Sources/Measurements

The FRB! system collects data from each clinical visit, including the number of letters read on a logarithm of the minimum angle of resolution (LogMAR) VA Chart (best of uncorrected, corrected or pinhole), treatment given, choroidal neovascular (CNV) lesion activity, as judged by the treating physician based on funduscopy, optical coherence tomography imaging or fluorescein angiography alone or in combination (an active grading indicated the presence of "intraretinal or subretinal fluid attributable to leak from choroidal neovascularisation lesion or fresh haemorrhage"), and ocular adverse events. Previous treatments received, lesion subtype as determined by the practitioner based on retinal angiography and lesion size (greatest linear dimension, GLD) were recorded during the baseline visit. Treatment decisions, including drug choice and treatment frequency, were at the discretion of the practitioner in consultation with the patient, thereby reflecting real-world practice.

We explored several avenues for assessing the early response. Most protocols for treating nAMD generally start with a loading of 3 injections of a VEGF inhibitor at monthly intervals regardless of the treatment regimen. [17, 18] Thus, the early response was specified to occur at the time the 4th injection was due. The metrics for measuring the early response and the expected relationship with long-term outcomes are described below:

1. **Achieving good vision,** defined as having ≥70 letters (20/40 vision)

2. **Absolute change in VA from baseline**, defined as the change in VA from baseline, was analysed as a continuous variable and as a categorical variable based on the following groups:
    1. *Early Loss:* ≤0 letter improvement i.e. loss of vision or no change in vision
    2. *Small Early Gain:* 1-5 letter improvement
    3. *Large Early Gain:* >5 letter improvement
3. **Time to CNV Inactivity**, defined by the lesion activity status. Following the definitions from a previous FRB! study,[19] we defined the following groups:
    1. *Short Induction:* Eye required ≤3 injections until the first grading of the CNV lesion as inactive
    2. *Long Induction:* Eye required >3 injections before the lesion was graded as inactive. This included eyes whose CNV lesion remained active throughout the 3 year study period.
4. **Maximum rate of VA change,** defined as the highest rate of change in VA between two successive injections until the 4th injection was due and converted to a standardised rate of letter change per 4 weeks. This rate of change was analysed as a continuous variable and as a categorical variable based on the following groups:
    1. *Rapid Loss:* Largest VA change between successive injections >5 letter loss per 4 weeks
    2. *Gradual Change:* Largest VA change between successive injections between -4 and 4 letters per 4 weeks
    3. *Rapid Gain:* Maximum of ≥5 letter improvement per 4 weeks.

Participants

Treatment-naïve eyes with nAMD tracked by the FRB! registry commencing anti-VEGF therapy between 1st January 2007 and 1st March 2014 were considered, thereby allowing all eyes the possibility of completing at least 3 years of follow-up at the time the analysis was conducted. For inclusion, eyes were also required to have received 3 monthly anti-VEGF injections as a loading dose to establish the early response and limit the possibility that poor early response was due to under-treatment. Completers were defined as eyes completing 3

years of follow-up while non-completers were eyes that did not complete 3 years of follow-up.

Outcome Measures

The primary outcome was the proportion of eyes achieving VA≥70 letters at 3 years. Secondary outcomes included the change in VA at 3 years and non-completion rates.

Statistical Analysis

Descriptive data included the mean, standard deviation (SD), median, 25th and 75th percentiles (Q1, Q3), and percentages where appropriate. Baseline demographics were compared using ANOVA, Kruskal-Wallis, t-test, Wilcoxon rank sum and Chi-square tests. Longitudinal generalised additive models were used to plot longitudinal visual outcomes over 3 years of treatment and included data from completers and non-completers. [20, 21]

The early response was analysed according to the 4 definitions described above. Logistic regression models were also performed with the VA at 3 years as a categorical variable (<70 letters vs. ≥70 letters) and odds ratios reported. Linear mixed-effects models were used to assess the relationship between the change in VA and final VA at 3 years and early response definitions. Since these early responses were likely to be correlated, separate models were fit for each definition. Injection frequency was analysed using Poisson regression models with an offset for log follow-up duration (days). Cox-proportional hazards models were used to assess non-completion rates and visualised using Kaplan-Meier survival curves.

Covariates for linear, Poisson and Cox-proportional hazards models also included adjustments for age, lesion size, lesion type (fixed-effects) and clustering by practice and patient (random-effects).

Baseline VA was not included as a covariate to avoid potential multicollinearity with the early responses. Instead, separate models were fitted with baseline VA instead of the early response to determine whether using the early response is better than simply using the baseline VA for predicting outcomes. Models were compared using marginal R^2 values for mixed-models.[22] We also report Akaike's Information Criterion (AIC) for model comparison where smaller values indicate better fit. Sensitivity analyses were conducted in which only

one eye per patient was analysed for bilateral patients; either the first presenting eye or the worse presenting eye if both eyes were diagnosed simultaneously.

Pairwise comparisons were performed using the Holm-Bonferroni adjustment where appropriate. A p-value of 0.05 was considered statistically significant.

All analyses were conducted in R version 3.3.2 using the *lme4* package (V1.1-13) for mixed-effects models and *coxme* package (V2.2-5) for Cox-proportional hazards models.[23-25]

Results

Study Population

This study included 2051 treatment-naïve eyes from 1828 patients (223 bilateral patients) that initiated treatment between 1st January 2007 and 1st March 2014. There were 762 (37%) eyes that did not complete 3 years of follow-up during the study period. The median (Q1, Q3) days until the 4th injection was 105 (91, 123) days. Baseline demographic characteristics partitioned by the categorical early response definitions set out above are summarised in Table 1.

Overall, there were 572 (28%) eyes with good VA (≥70 letters, Snellen equivalent 20/40) at baseline; at the 4th injection this number had increased to 882 (43%) eyes. Approximately half of eyes underwent a longer period of monthly injections after the initial 3 loading injections (1067 eyes; 52%), including 222 eyes who either remained active by the end of the 3 year follow-up (69 eyes) or at time of non-completion (153 eyes).

Eyes in the Large Early Gain group had significantly lower mean [SD] baseline VA (49.6 [18.1] letters) compared with the Early Loss (60.1 [19.1] letters, $P < 0.001$) and the Small Early Gain (63.1 [14.4] letters, $P < 0.001$) groups. However, we note that eyes in the Early Loss group had similar baseline VA to the Small Early Gain group ($P = 0.13$). Lesion sizes were significantly smaller in eyes with good VA at 4th injection (median [Q1, Q3]: 1934µm [1124, 2800] vs. 2500µm [1500, 3500], $P < 0.001$) and in eyes with shorter time to inactivity (median [Q1, Q3]: 2000 [1298, 3000] µm vs. 2500 [1500, 3500] µm, $P < 0.001$).

The overall mean (SD) early change in VA was 6.1 (13.2) letters; the overall mean (SD) maximal change in VA between successive injections was 5.2 (14.6) letters.

Achieving Good Vision at 3 Years

The association between categorical early response definitions and achieving good vision (≥70 letters, 20/40) at 3 years is summarised in Table 2. Of the 1289 eyes that completed 3 years of treatment, 608 (47%) had good VA after 3 years of treatment. Overall, achieving good VA by the 4th injection was the best predictor of good vision at 3 years ($R^2 = 0.30$), outperforming the model using baseline VA ($R^2 = 0.17$).

Eyes were significantly more likely to achieve good VA (odds ratio [95%CI]) if they had already achieved good vision by the 4th injection (9.8 [6.5, 14.7], $P < 0.001$ for VA≥70 vs. VA<70 letters by 4th injection), achieved small early or large early gains (1.8 [1.2, 2.6], $P = 0.002$ and 1.8 [1.3, 2.5], $P < 0.001$ for small and large early gains vs. early loss), had a short induction (1.6 [1.2, 2.1], $P < 0.001$ for short vs. long induction), or experienced gradual change or rapid gain (1.7 [1.1, 2.6], $P = 0.015$ and 1.6 [1.0, 2.3], $P = 0.018$ for gradual change and rapid gain vs. rapid loss). However, with the exception of achieving good vision by the 4th injection, the remaining early response definitions failed to outperform the baseline model. Sensitivity analyses including only one eye per patient yielded the same result (supplementary material S1).

Approximately three quarters (73.0%) of eyes with good VA at the 4th injection maintained good vision after 3 years of treatment. Encouragingly, an additional 149/1289 (22.6%) eyes that had <70 letters at the 4th injection achieved >70 letters at year 3.

Visual Acuity Outcomes at 3 Years

The association between early response definitions and change in VA at 3 years is summarised in Table 3. Longitudinal VA outcomes through 3 years for categorical early response variables are shown in Figure 1. Overall, the model using the absolute change in VA at the 4th injection (continuous variable) provided the best fit ($R^2 = 0.37$) for predicting the

long-term change in VA, outperforming the model using baseline vision instead of the early response ($R^2 = 0.20$).

Eyes in the Early Loss group at the 4th injection had worse vision (mean VA change [95% CI]) at 3 years (-5.9 [-7.5, -4.3] letters) than the Small Early Gain (0.7 [-0.9, 2.3] letters, $P < 0.001$) and Large Early Gain groups (12.8 [11.4, 14.1], $P < 0.001$). Applying these same categories for VA change at 3 years (Figure 2), 68% of eyes that experienced Early Loss had VA loss at the end of the third year of treatment; these eyes had a relatively high (mean [SD]) baseline VA (64.4 [16.2]). The remaining eyes with Early Loss went on to achieve a small (14%) or large (18%) gain in vision despite this early loss, possibly indicating a delayed response. Similarly, 71% of eyes in the Large Early Gain group maintained their large VA gain at 3 years. Only 20% of eyes in the Small Early Gain group had a 1-5 letter gain at 3 years, with the remaining 80% split evenly between VA loss and large gains.

Visual acuity at 3 years (mean VA [SD]) was significantly worse for eyes in the Early Loss group (57.4 [20.7]) than the Small Early Gain (65.0 [17.2], $P < 0.001$) and Large Early Gain groups (64.7 [17.6], $P < 0.001$). Eyes in the Large Early Gain group had a significantly greater improvement in vision at 3 years compared with the Small Early Gain group ($P < 0.001$) although the VA at 3 years was similar for these 2 groups ($P = 0.826$).

When eyes were grouped by early maximal rate of VA change, similar patterns were observed whereby the Rapid Loss, Gradual Change, and Rapid Gain groups performed similarly to the Early Loss, Small Early Gain and Large Early Gain groups respectively (Table 3).

Eyes with shorter induction had significantly better VA (mean [SD]) at the end of 3 years (65.3 [17.9] letters vs. 59.6 [20.3] letters, $P < 0.001$) although there was no significant difference in VA change ($P = 0.145$).

Injection Frequency

Overall, eyes completing 3 years of follow-up received a median (Q1, Q3) of 19 (15, 23) injections. More frequent injections were associated with higher VA change at 3 years (model coefficient [95%CI]: 0.31 [0.18, 0.44] letters at 3 years per injection, $P < 0.001$). We did not

find an association between VA change at the 4th injection (continuous: P = 0.750 and categorical: P = 0.754) or maximum change of VA (continuous: P = 0.088 and categorical: P = 0.345) with the number of injections.

Non-completion

Change in VA at time of dropout, non-completion rates and their association with the early response are summarised in Table 4. Overall, 762 (37%) eyes did not complete 3 years of follow-up during the study period. Doctor-reported reasons for non-completion were available for 311 eyes and included patient going to another doctor (100 eyes [32%]), further treatment futile (79 eyes [25%]), patient deceased (57 eyes [19%]), patient declined further treatment (44 eyes [14%]), treatment successful (26 eyes [8%]) and medically contraindicated (5 eyes [2%]).

Visual outcomes were generally worse compared with completers, although early response groups followed similar trends. At last visit, higher VA (mean [SD]) was observed in eyes with VA≥70 letters at the 4th injection (72.1 [13.4] vs. 43.0 [23.0] letters), small or large early VA gains (59.0 [23.4] and 55.6 [22.3] vs. 46.1 [26.2] letters for small and large early gains vs. early loss), short induction (56.0 [24.0] vs. 50.0 [24.7] letters for short vs. long induction) and gradual VA change or rapid VA gains (55.2 [25.3] and 54.3 [23.1] vs. 44.2 [25.4] letters for gradual change and rapid gain vs. rapid loss). As with completers, 75% of eyes achieving good vision at the 4th injection retained good vision at time of last observation.

Survival curves for non-completion over time by early response group are presented in Figure 3. Risk of non-completion (hazards ratio, HR [95% CI]) was significantly reduced when VA was ≥70 letters at the 4th injection (0.6 [0.5, 0.7] for VA≥70 vs. VA<70 at the 4th injection, P < 0.001), VA gains at the 4th injection were greater (0.8 [0.6, 0.9], P = 0.018, and 0.9 [0.7, 1.0], P = 0.100, for Small and Large Early Gain vs. Early Loss; global test, P = 0.016).

Discussion

This study explored several metrics for describing the early response to anti-VEGF treatment for nAMD and their ability to predict 3-year outcomes. We studied whether these early response definitions might predict long-term visual acuity outcomes better than the baseline visual acuity.

Eyes with VA≥70 letters (Snellen equivalent of 20/40) at the time of the 4th injection were almost 10 times more likely have good vision at 3 years than eyes with VA<70 letters at the 4th injection. Furthermore, although baseline vision was also a strong predictor of good visual acuity at 3 years, this relationship was not as strong as the visual acuity at the 4th injection.

Eyes that experienced early VA loss or small gain in the present study had somewhat similar baseline VA (60.1 and 63.1 letters respectively) but different outcomes at the 4th injection and at 3 years. Similar observations have been reported previously in DME for early moderate (5-9 letter gain) and suboptimal (<5 letter gain) VA gain groups. [26] Eyes that lost vision by the 4th injection had a mean loss of 1 line of vision at 3 years. For eyes that did not complete 3 years of treatment, there was a loss of almost 2 lines at time of dropout. In contrast, eyes that experienced a small early VA gain finished with the same visual acuity as eyes that achieved large early visual acuity gains (65.0 and 64.7 letters respectively) and were similarly likely to achieve good vision at 3 years. In addition, 18% of eyes that experienced early VA loss went on to gain more than 1 line of vision at 3 years, indicating a delayed response to anti-VEGF treatment. A post-hoc analysis of the CATT cohort reported 27% of eyes showing a loss of ≥1 line at 12 weeks went on to gain ≥1 line at 2 years. [13] Thus, it may be prudent to persist with anti-VEGF treatment even if the early response is poor in the absence of effective alternative treatments.

Measuring the maximum rate of VA change between successive injections was a novel way to assess the early response. We observed that approximately three quarters of eyes either gained (54%) or lost (18%) more than 5 letters at least once between 2 successive injections, with only 28% experiencing more gradual changes between successive injections. However, the maximal rate of change and raw early VA change definitions provided somewhat similar information, and the models using early VA change provided a better fit than the maximal rate of change.

Lesion activity, or shorter time to lesion inactivation, may be another useful marker of early treatment response. Eyes with a shorter time to lesion inactivity (3 or fewer injections) had better vision than eyes requiring more than 3 injections, both at baseline (57.8 vs 53.9 letters respectively) and at 3 years (65.3 vs. 59.6 letters respectively). They were also more likely to have good vision (70 letters, 20/40) at 3 years although the change in VA at 3 years was not significantly different (P = 0.091). A previous analysis of 12-month outcomes found eyes with highly active lesions performed similarly to those with less active lesions, [27] however a longer term analysis is warranted to clarify the relationship between highly active lesions and visual outcomes.

We found that improvement in visual acuity up to the 4th injection of VEGF inhibitors was the most robust clinical predictor of visual acuity 3 years after starting treatment. Previous studies have also found greater predictive power between the 12 week change in VA with the 1 and 2 year outcomes compared with only using the baseline VA.[13] This is probably because the disease is still largely VEGF-driven in these cases with a good early response. Cases which do not respond so well may be also be driven by other, less reversible, pathological processes such as inflammation, fibrosis and macular atrophy. [13]

The present study has some limitations. Treatment schedules after the initial loading phase, which might have influenced long-term outcomes,[17, 28] were at the discretion of the physician and patient although most of the FRB! database practitioners use a treat and extend regimen.[29, 30] It is however possible that patients with inferior initial responses may have subsequently been less compliant or extended out by the physician and suffered inferior outcomes as a result. Eyes with good VA at the 4th injection, tended to have better 3-year outcomes, and also on average, received more injections. Overall, more injections are associated with better visual acuity outcomes. [29] Still, eyes that were continued on monthly injections after the 3 initial monthly injections due to persistent activity – and thus had a high total number of injections - had worse outcomes at 3 years, possibly because their lesions were more active. Anti-VEGF drug type was not considered in the present analysis because previous studies have found no substantial difference between ranibizumab and aflibercept. [31] Nor did we report switching rates as aflibercept was not yet available as a treatment option for most of our follow-up period. We note that while switching treatments may be a possible strategy when the early response is poor, there is currently little if any evidence that switching anti-VEGF agents provides any obvious benefit. [32]

High non-completion rates are common in observational studies, and this study was no exception; 37% of eyes did not complete 3 years of follow-up during the study period. Reasons for non-completion were reported for more than a third of the non-completers, with most due to reasons that were not linked with efficacy. Around 40% of the eyes with a recorded reason for non-completion were discontinued because further treatment was futile or the patient declined further treatment. Patients were more likely to drop out if they experienced early VA loss or their VA was less than 70 letters at the 4th injection. The change in visual acuity at time of dropout between early response groups followed broadly similar patterns to those observed in the completers, although the final vision at time of dropout for the early response groups was, on average, 1-2 lines lower than their respective completers.

In conclusion, the early response, particularly attainment of good vision and change in visual acuity by the 4th injection, was more strongly associated with 3 year visual outcomes than visual acuity at the time of starting treatment. As treatment protocols for nAMD generally begin with 3 monthly injections, the response during this standardised period of treatment may be useful to guide further treatment. [33]

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Figure Captions

Figure 1. Predicted visual acuity (VA) over time from longitudinal generalised additive models partitioned by A) whether VA was ≥70 letters at the 4th injection, B) absolute change in VA at the 4th injection, C) length of the induction period and D) maximum rate of VA change between successive injections. These models included data from completers and non-completers.

Figure 2. Percentage of eyes partitioned by (A) VA change at the 4th injection and at 3 years, and (B) VA change at the 4th injection, VA<70 or ≥70 letters at the 4th injection (<70 and ≥70 respectively, labelled above bars), and VA<70 or ≥70 letters at 3 years. Categories for VA change included early loss (<0 letter improvement), small gain (1-5 letter improvement) and large gain (>5 letter improvement). The number of eyes in each early VA change group is shown above the bars.

Figure 3. Kaplan-Meier survival curves of time to non-completion partitioned by A) whether VA was ≥70 letters at the 4th injection, B) absolute change in VA at the 4th injection, C) length of the induction period and D) maximum rate of VA change between successive injections

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Table 1. Demographic characteristics of eyes grouped by their early response to treatment.

	Overall	Good Vision Achieved by 4th Injection		Good Vision Achieved by 4th Injection			Time to Inactive CNV		Maximum Rate of VA Change		
		VA <70 Letters	VA ≥70 Letters	Early Loss	Small Early Gain	Large Early Gain	Short	Long*	Rapid Loss	Gradual Change	Rapid Gain
Eyes	2051	1169	882	682	422	947	984	1067	368	568	1115
Patients	1828	1088	831	647	412	897	907	1002	352	550	1056
Females, %	61.5%	62.0%	60.8%	59.5%	62.8%	62.3%	62.2%	60.8%	61.4%	61.6%	61.4%
Baseline Age (SD)	79.6 (8.2)	80.7 (7.9)	78.3 (8.3)	79.7 (8.6)	79.4 (7.8)	79.8 (8)	80.7 (7.8)	78.7 (8.4)	79.4 (8.6)	79.2 (8.3)	80.0 (8.0)
Baseline VA (SD)	55.9 (18.7)	46.6 (17.8)	68.1 (11.2)	60.1 (19.1)	63.1 (14.4)	49.6 (18.1)	57.8 (18.4)	54.1 (18.8)	60.3 (16.4)	61.5 (19.2)	51.6 (18.0)
≥70 Letters, n (%)	572 (27.9%)	82 (7.0%)	490 (55.6%)	277 (40.6%)	189 (44.8%)	106 (11.2%)	318 (32.3%)	254 (23.8%)	136 (37.0%)	255 (44.9%)	181 (16.2%)
≤35 Letters, n (%)	308 (15.0%)	289 (24.7%)	19 (2.2%)	84 (12.3%)	23 (5.5%)	201 (21.2%)	124 (12.6%)	184 (17.2%)	36 (9.8%)	66 (11.6%)	206 (18.5%)
Baseline Lesion Size,	2250	2500	1934	2314	2200	2200	2000	2500	2200	2250	2250
Median µm (Q1, Q3)	(1439, 3200)	(1500, 3500)	(1124, 2800)	(1458, 3300)	(1300, 3158)	(1500, 3200)	(1298, 3000)	(1500, 3500)	(1400, 3306)	(1394, 3300)	(1500, 3199)
Lesion Type, %											
Occult	56.6%	55.4%	58.2%	55.7%	64.2%	53.9%	57.5%	55.8%	60.1%	55.3%	56.1%
Minimally Classic	14.2%	14.5%	13.9%	14.5%	11.1%	15.4%	12.7%	15.7%	13.0%	13.4%	15.1%
Predominantly Classic	20.5%	21.6%	18.9%	21.1%	16.45%	21.9%	20.7%	20.2%	20.1%	20.1%	20.8%
Other	7.3%	7.4%	7.1%	7.3%	7.3%	7.3%	7.4%	7.2%	6.2%	9.0%	6.85%
Not Recorded	1.4%	1.0%	1.8%	1.3%	0.9%	1.6%	1.6%	1.1%	0.5%	2.3%	1.2%

* Includes 222 persistently active eyes whose lesion has yet to be graded as inactive by the end of completing 3 years of follow-up (69 eyes) or at their most recent visit if they did not complete 3 years of follow-up (153 eyes)

Table 2. Association between definitions of early response and achieving good vision (≥70 letters) at 3 years. Odds ratios and their respective p-values are presented only for categorical variables. Significant p-values are highlighted in bold.

Categorical Early Response Definitions	VA<70 Letters at 3 Years, n (%)	VA≥70 Letters at 3 Years, n (%)	Odds Ratio for Achieving ≥70 Letters at 3 Years (95% CI)	P-value	Marginal R^2	AIC
Overall	681 (53%)	608 (47%)	-			
Good VA at Baseline						
VA <70 Letters	574 (64%)	321 (36%)	1	**<0.001**	0.17	1606
VA ≥70 Letters	107 (27%)	287 (73%)	4.50 (3.30, 6.14)			
Good VA Achieved by 4th Injection						
VA <70 Letters	511 (77%)	149 (23%)	1	**<0.001**	0.30	1433
VA ≥70 Letters	170 (27%)	459 (73%)	9.78 (6.50, 14.70)			
Absolute Change in VA from Baseline at 4th Injection						
Early Loss	248 (62%)	152 (38%)	1	**<0.001***	0.08	1711
Small Early Gain	135 (48%)	148 (52%)	1.75 (1.17, 2.61)			
Large Early Gain	298 (49%)	308 (51%)	1.76 (1.25, 2.45)			
Time to Inactive CNV						
Short Induction	300 (47%)	341 (53%)	1.59 (1.23, 2.07)	**<0.001**	0.07	1715
Long Induction	381 (59%)	267 (41%)	1			
Maximum Rate of VA Change						
Rapid Loss	141 (62%)	86 (38%)	1	**0.011†**	0.07	1720
Gradual Change	165 (49%)	175 (51%)	1.70 (1.09, 2.64)			
Rapid Gain	375 (52%)	347 (48%)	1.55 (1.05, 2.30)			

Pairwise comparisons with Holm-Bonferroni adjustment for multiple comparisons:

* Early Loss vs. Small Early Gain ($P = 0.002$), Early Loss vs. Large Early Gain ($P < 0.001$), Small Early Gain vs. Large Early Gain ($P = 0.986$)

† Rapid Loss vs. Gradual Change (P = 0.015), Rapid Loss vs. Rapid Gain (P = 0.018), Gradual Change vs. Rapid Loss (P = 0.523)

Table 3. Association between different definitions of early response and 3 year outcomes. Regression coefficients from multiple regression models are reported for continuous variables and visual acuity (VA) outcomes are reported for categorical variables. All models include adjustments for age, lesion size and lesion type (fixed effects), and practice and patient identifier (random effects). Significant p-values are highlighted in bold.

Baseline VA Model	**Association with year 3 VA**			**Association with year 3 ΔVA**				
	Model Coefficient	**Standardised Coefficient**	**P-value**	**Model Coefficient**	**Standardised Coefficient**	**P-value**	**Marginal R^2**	**AIC**
Baseline VA	-0.55	10.29	**<0.001**	-0.45	-8.39	**<0.001**	0.20	10851
Continuous Early Response Variables	**Association with year 3 VA**			**Association with year 3 ΔVA**				
	Model Coefficient	**Standardised Coefficient**	**P-value**	**Model Coefficient**	**Standardised Coefficient**	**P-value**	**Marginal R^2**	**AIC**
Absolute Change in VA from Baseline at 4th Injection	0.21	2.64	**<0.001**	0.86	10.76	**<0.001**	0.37	10520
Maximum rate of VA Change per 4 Weeks	0.06	0.92	**<0.001**	0.38	5.80	**<0.001**	0.12	10951
Categorical Early Response Definitions	**Association with year 3 VA**			**Association with year 3 ΔVA**				
	VA 3 Years (SD)	**Adjusted VA 3 Years (95% CI)**	**P-value**	**ΔVA 3 Years (95% CI)**	**Adjusted ΔVA 3 Years (95% CI)**	**P-value**	**Marginal R^2**	**AIC**
Good VA Achieved by 4th Injection								
VA <70 Letters	52.8 (20.3)	53.5 (51.8, 55.1)	**<0.001**	3.8 (2.3, 5.4)	4.4 (2.8, 6.0)	0.795	0.02	11099
VA ≥70 Letters	72.5 (11.7)	71.8 (70.1, 73.4)		4.9 (3.7, 6.0)	4.7 (3.1, 6.3)			
Absolute Change in VA from Baseline at 4th Injection								

Early Loss	57.2 (22.2)	57.9 (55.5, 60.3)	**<0.001***	-5.9 (-7.5, -4.3)	-5.6 (-7.2, -3.9)	**<0.001****	0.23	10794
Small Early Gain	65.0 (17.2)	64.4 (61.7, 67.1)		0.7 (-0.9, 2.3)	0.7 (-1.3, 2.6)			
Large Early Gain	64.7 (17.6)	64.7 (62.6, 66.8)		12.8 (11.4, 14.1)	12.8 (11.4, 14.2)			
Time to Inactive CNV								
Short Induction	65.3 (17.9)	64.9 (62.9, 66.9)	**<0.001**	5.3 (3.9, 6.6)	5.3 (3.7, 6.8)	0.145	0.02	11097
Long Induction	59.6 (20.3)	60.1 (58.1, 62.1)		3.4 (2.0, 4.9)	3.7 (2.2, 5.3)			
Maximum Rate of VA Change per 4 Weeks								
Rapid Loss	57.4 (20.7)	58.0 (55.1, 60.9)	**<0.001†**	-5.2 (-7.6, -2.8)	-4.7 (-7.0, -2.4)	**<0.001††**	0.14	10937
Gradual Change	63.4 (19.9)	62.8 (60.2, 65.3)		-0.7 (-2.1, 0.7)	-0.9 (-2.8, 1.0)			
Rapid Gain	63.6 (18.4)	63.7 (61.6, 65.7)		9.7 (8.4, 11.0)	9.7 (8.4, 11.1)			

Pairwise comparisons with Holm-Bonferroni adjustment for multiple comparisons:

* Early Loss vs. Small Early Gain ($P < 0.001$), Early Loss vs. Large Early Gain ($P < 0.001$), Small Early Gain vs. Large Early Gain ($P = 0.826$)

** Early Loss vs. Small Early Gain ($P < 0.001$), Early Loss vs. Large Early Gain ($P < 0.001$), Small Early Gain vs. Large Early Gain ($P < 0.001$)

† Rapid Loss vs. Gradual Change ($P = 0.006$), Rapid Loss vs. Rapid Gain ($P < 0.001$), Gradual Change vs. Rapid Loss ($P = 0.452$)

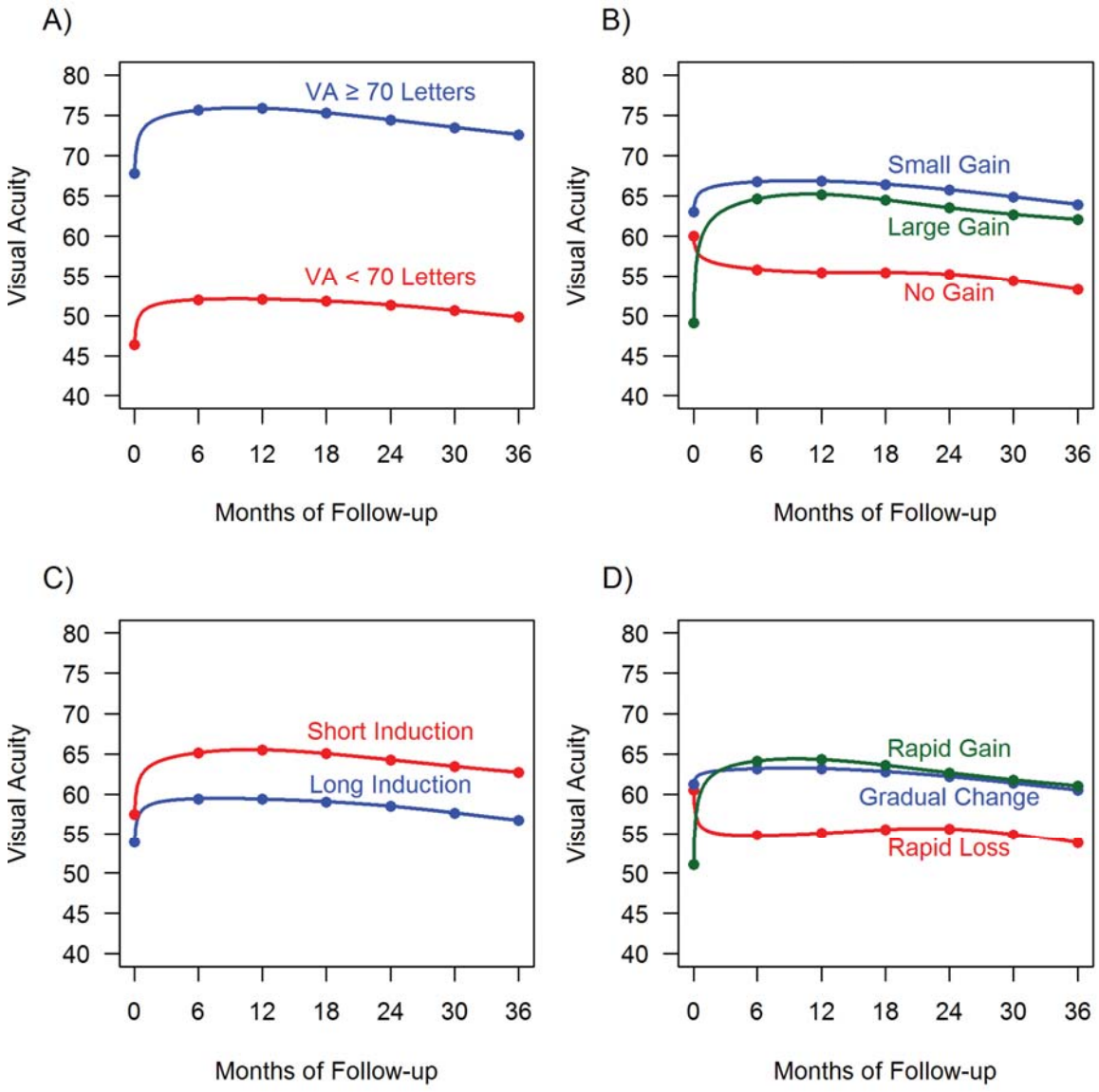
†† Rapid Loss vs. Gradual Change ($P = 0.007$), Rapid Loss vs. Rapid Gain ($P < 0.001$), Gradual Change vs. Rapid Loss ($P < 0.001$)

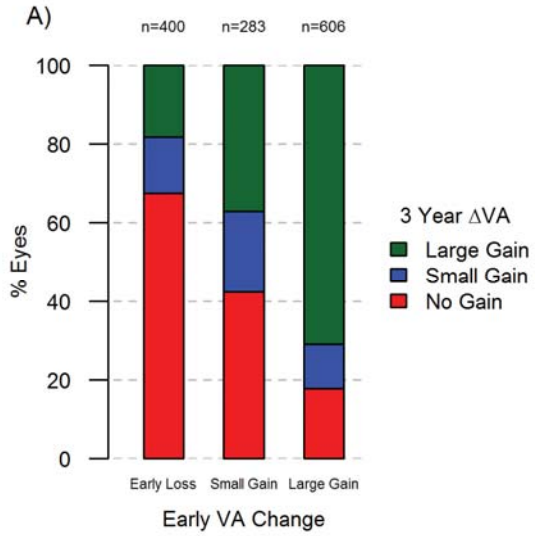
Table 4. Visual acuity, change in VA and the proportion of eyes with VA≥70 letters at time of dropout, non-completion rates and their association with different definitions of early response. Hazards ratios for non-completion and their respective p-values are presented only for categorical variables. Significant p-values are highlighted in bold.

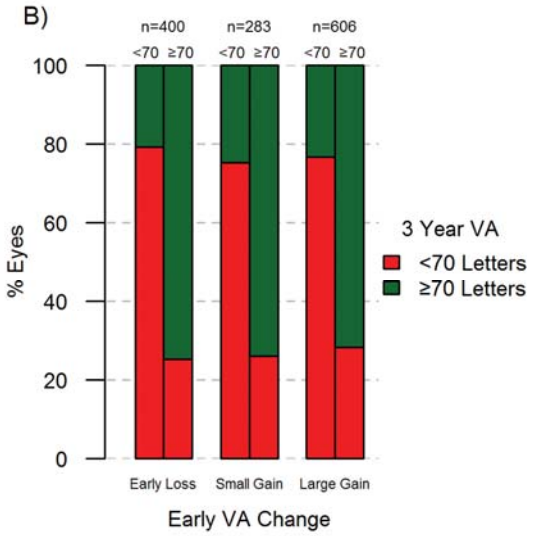
Categorical Early Response Definition	VA at Time of Dropout (SD)	ΔVA at Time of Dropout (95% CI)	VA≥70 Letters, n (%)	Non-completion Rate, n / N (%)	Hazards Ratio for non-completion (95% CI)	P-value
Overall	52.7 (24.5)	0.6 (-0.9, 2.0)	243 (32%)	762 / 2051 (37%)	-	-
Good VA at Baseline						
VA<70 Letters	46.9 (24.2)	2.0 (0.3, 3.8)	112 (19%)	584 / 1479 (39%)	1	**0.003**
VA≥70 Letters	71.6 (13.8)	-4.3 (6.3, -2.3)	131 (74%)	178 / 572 (31%)	0.77 (0.63, 0.90)	
Good VA by 4th Injection						
VA<70 Letters	43.0 (23.0)	-0.5 (-2.5, 1.4)	52 (10%)	509 / 1169 (44%)	1	**<0.001**
VA≥70 Letters	72.1 (13.4)	2.8 (0.9, 4.7)	191 (75%)	253 / 882 (29%)	0.61 (0.51, 0.71)	
Absolute Change in VA from Baseline at 4th Injection						
Early Loss	46.1 (26.2)	-9.7 (-11.8, -7.6)	78 (28%)	282 / 682 (41%)	1	**0.016***
Small Early Gain	59.0 (23.4)	-1.8 (-4.4. 0.9)	61 (44%)	139 / 422 (33%)	0.75 (0.56, 0.93)	
Large Early Gain	55.6 (22.3)	10.0 (8.0, 12.1)	104 (30%)	341 / 947 (36%)	0.85 (0.69, 1.01)	
Time to Inactive CNV						
Short Induction	56.0 (24.0)	2.3 (0.3, 4.3)	129 (38%)	343 / 984 (35%)	0.90 (0.74, 1.05)	0.196
Long Induction	50.0 (24.7)	-0.9 (-2.9, 1.2)	114 (27%)	419 / 1067 (39%)	1	
Maximum Rate of VA Change						
Rapid Loss	44.2 (25.4)	-12.4 (-15.8, -9.0)	32 (23%)	141 / 368 (38%)	1	0.157
Gradual Change	55.2 (25.3)	-2.3 (-4.3, -0.3)	93 (41%)	228 / 568 (40%)	1.05 (0.78, 1.32)	
Rapid Gain	54.3 (23.1)	6.9 (4.9, 8.9)	118 (30%)	393 / 1115 (35%)	0.90 (0.69, 1.11)	

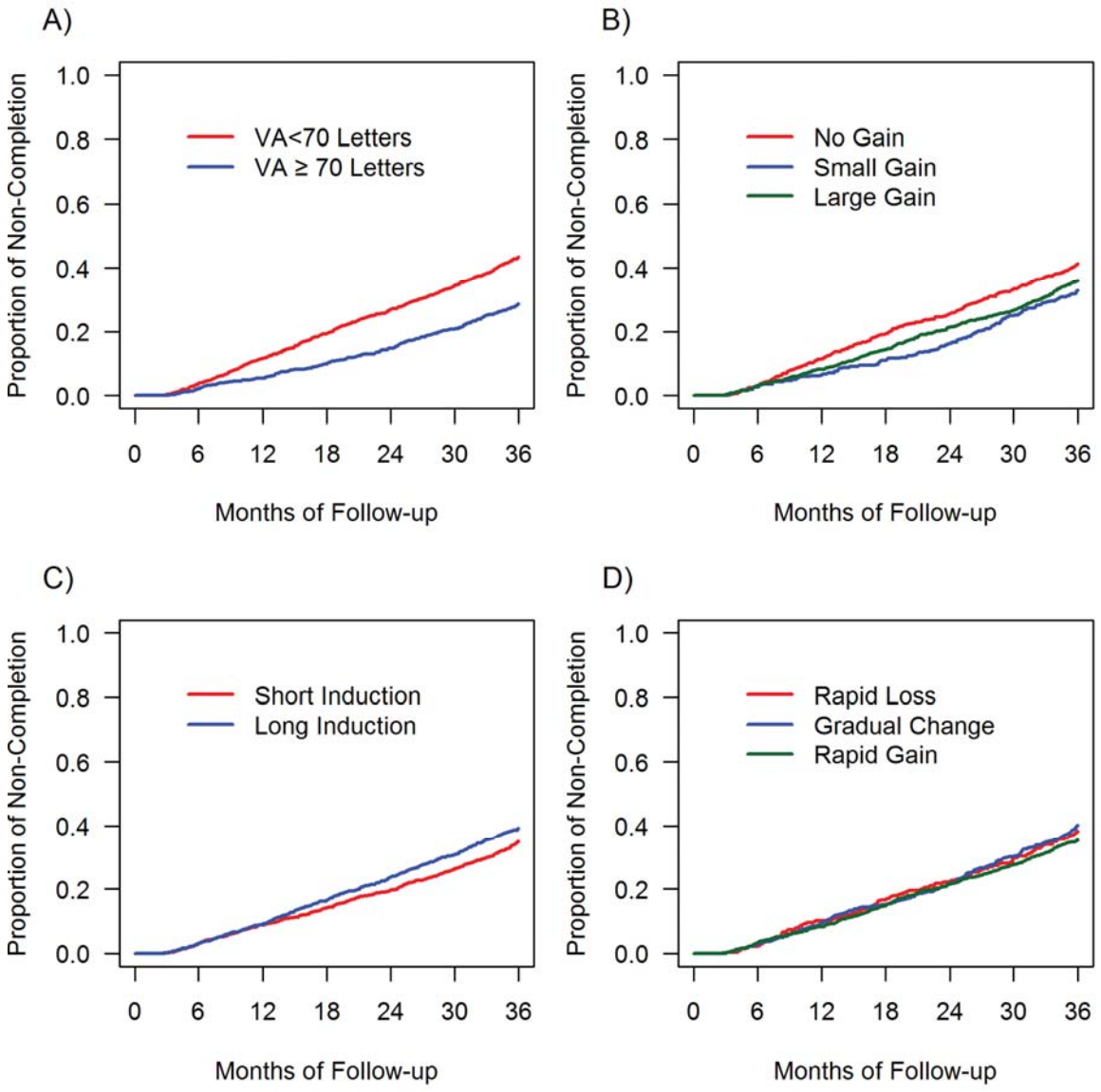
Pairwise comparisons with Holm-Bonferroni adjustment for multiple comparisons:

* Early Loss vs. Small Early Gain (P = 0.018), Early Loss vs. Large Early Gain (P = 0.100), Small Early Gain vs. Large Early Gain (P = 0.206)


A)
Visual Acuity
80
75
70
65
60
55
50
45
40
VA ≥ 70 Letters
VA < 70 Letters
0
6
12
18
24
30
36
Months of Follow-up
B)
Visual Acuity
Small Gain
Large Gain
No Gain
Months of Follow-up
C)
Visual Acuity
Short Induction
Long Induction
Months of Follow-up
D)
Visual Acuity
Rapid Gain
Gradual Change
Rapid Loss
Months of Follow-up






A)
Proportion of Non-Completion
1.0
0.8
0.6
0.4
0.2
0.0
VA<70 Letters
VA ≥ 70 Letters
0
6
12
18
24
30
36
Months of Follow-up
B)
Proportion of Non-Completion
No Gain
Small Gain
Large Gain
Months of Follow-up
C)
Proportion of Non-Completion
Short Induction
Long Induction
Months of Follow-up
D)
Proportion of Non-Completion
Rapid Loss
Gradual Change
Rapid Gain
Months of Follow-up

The early response to treatment for neovascular age-related macular degeneration is highly associated with treatment outcomes at 3 years and may provide a useful marker for guiding long-term treatment decisions.