ASSOCIATION BETWEEN ANATOMICAL AND CLINICAL OUTCOMES OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR

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Purpose: Assess the relationship between subretinal fluid (SRFL), intraretinal fluid, and visual outcomes of neovascular age-related degeneration in routine clinical practice.

Methods: Treatment-naive eyes enrolled in the Fight Retinal Blindness! registry after January 2017 were identified. Lesion activity was graded at each visit as inactive, active not SRFL only (A-NSRFL only), or active SRFL only (A-SRFL only). Eyes were grouped based on initial activity as follows: 1) *initially A-NSRFL only* or 2) *initially A-SRFL only*, and their predominant activity status over 12 months was as follows: 1) *mostly inactive*, 2) *mostly A-NSRFL only,* or 3) *mostly A-SRFL only*.

Results: Seven hundred and three eyes were eligible for analysis. *Initially A-NSRFL only* had a similar adjusted mean 12-month visual acuity change to *initially A-SRFL* eyes (5.7 vs. 6.9 letters; *P* = 0.165), but their final visual acuity was worse (62.5 vs. 67.5 letters at 12 months; *P* = 0.003). The adjusted mean 12-month visual acuity change between the predominant activity groups was significantly different (*P* = 0.005), with *mostly inactive* (7.6 letters) and *mostly A-SRFL only* (7.5 letters) eyes gaining more than *mostly A-NSRFL only* eyes (3.6 letters).

Conclusion: Eyes with SRFL only had similar outcomes at 1 year to eyes that were mostly inactive. Intraretinal fluid was associated with worse visual outcomes, highlighting the importance of distinguishing between intraretinal fluid and SRFL when managing neovascular age-related degeneration.

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Individualized treatment regimens for neovascular age-related macular degeneration (nAMD) with vascular endothelial growth factor inhibitors, such as pro re nata and treat-and-extend, generally aim to inactivate the choroidal neovascular lesion with the fewest injections.[1,2] However, recent studies have reported that some level of fluid, particularly subretinal fluid (SRFL), may be tolerated or even beneficial.[3–5] The phase IV FLUID study reported that eyes in which some SRFL was tolerated achieved similar outcomes with fewer injections than eyes treated for complete resolution of all SRFL.[4] Completely drying the retina may also increase the risk of macular atrophy (MA), a major irreversible cause of poor long-term outcomes.[6–9]

Intraretinal fluid (IRFL) on the other hand has been reported to be associated with poorer visual outcomes and an increased risk of MA.[5,10,11] Thus, the effects of persistent retinal fluid in eyes treated for choroidal neovascularization may depend on whether the fluid is intraretinal or subretinal.

There is currently no evidence apart from clinical trials that distinguishes the effects of SRFL and IRFL. Previous research from the Fight Retinal Blindness! (FRB!) project using data from routine clinical practice

reported an increased risk of MA when lesions were predominantly dry and an increased risk of subretinal fibrosis when lesions were predominantly active,[8,12] although the data collection system made no distinction between SRFL and IRFL. The present study aimed to establish the relationship between anatomical and visual outcomes and determine whether the findings from RCTs on SRFL and IRFL are consistent with routine clinical practice.

Materials and Methods

Study Design and Setting

Eligible patients were identified from the observational FRB! database.[13] The FRB! database tracks clinical outcomes from routine clinical practice for patients with nAMD and is compliant with the International Consortium for Healthcare Outcome Measurement's minimum standard set of treatment outcomes for macular degeneration.[14]

Ethics approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists; the University of Sydney; the French Institutional Review Board (Société Française d'Ophtalmologie IRB); Singhealth, Singapore; the Clinical Research Ethics Committee of Aragon,

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Spain; and the Cantonal Ethics Committee, Zurich, Switzerland. Patients from Australia, France, Ireland, New Zealand, Singapore, Spain, and Switzerland were included.

Data Sources/Measurements

Data recorded from each clinical visit by the treating practitioner included the number of letters read on a logarithm of the minimum angle of resolution (logMAR) visual acuity chart (best of corrected, uncorrected, or pinhole), treatment given, and ocular adverse events. Macular atrophy and subretinal fibrosis (SF) were graded at each visit as either subfoveal, extrafoveal, or not present based on clinical examination, optical coherence tomography, or dye angiography, alone or in combination. Previous treatments received and angiographic lesion subtypes were recorded at the baseline visit. We do not provide definitions or specify retreatment criteria for treatment regimens in this analysis as these decisions were at the discretion of the practitioner in consultation with the patient with no intervention by the investigators, reflecting routine clinical practice.

Before January 2017, clinicians graded choroidal neovascular lesion activity, where an active grading indicated the presence of "intraretinal or subretinal fluid attributable to leak from choroidal neovascularization lesion or fresh hemorrhage." After this date, clinicians were required to grade activity as being either "inactive," "active (any combination of IRFL, SRFL, or hemorrhage excluding SRFL only)," hereafter referred to as "active not SRFL only" (A-NSRFL only), or "active SRFL only" (A-SRFL only), thereby distinguishing between SRFL only and any combination of other retinal fluid excluding SRFL only.

Study Population and Groups

We included treatment-naive eyes with nAMD who were enrolled in the FRB! database from January 2017 because their visit history would contain the new lesion activity gradings that distinguish between SRFL only and other retinal fluid. Eyes were also required to have received a minimum of 3 injections within the 12-month period to establish ongoing treatment and have a sufficient sample of lesion activity gradings for each patient. Completers were defined as those who completed at least 12 months of follow-up.

Eyes were allocated to either "*initially A-NSRFL only*" or "*initially A-SRFL only*." We also partitioned eyes based on their most common lesion activity status experienced throughout their 12-month follow-up as being either 1) *mostly inactive*, 2) *mostly A-NSRFL*

only, or 3) *mostly A-SRFL only*. In the event of a tie between two and three activity statuses, priority was given to *mostly A-SRFL only*, followed by *mostly A-NSRFL only*, with *mostly inactive* given the lowest priority because *A-SRFL only* and *A-NSRFL only* are both fluid groups. A sensitivity analysis was performed using the same classifications but using only visits occurring during the maintenance phase (3–12 months). Eyes that did not have visits during this period were not included in the sensitivity analysis.

Outcome Measures

The primary outcome measure was the mean change in visual acuity between the 2 sets of groups over the 12-month period. Secondary outcomes included the frequency of injections and visits, the proportion of eyes at <8 weeks and ≥12 weeks treatment intervals, rate of development of macular atrophy and subretinal fibrosis, the proportion of eyes in each lesion activity state (inactive, A-NSRFL only, or A-SRFL only) over time, and the cumulative time spent in each activity state.

Statistical Analysis

Descriptive data included the mean, SD, median, 25th and 75th percentiles (Q1 and Q3), and percentages as appropriate. Baseline demographic and clinical characteristics were compared between activity groups using *t*-tests, Wilcoxon rank-sum tests, chi-square tests, ANOVA, and Kruskal–Wallis tests where appropriate. Raw, unadjusted outcomes were reported using the last observation carried forward for noncompleters.

Visual outcomes between activity groups over 12 months of treatment were assessed using mixed effects longitudinal generalized additive models and included visits from baseline through 12 months from all eyes, regardless of whether they completed 12 months of follow-up.

The development of new MA and SF over the 12-month period was visualized using Kaplan–Meier survival curves. Cox proportional hazards models were used to assess the hazards ratio between activity groups. Eyes that were diagnosed with MA or SF at baseline were excluded from this analysis. We did not distinguish between extrafoveal and subfoveal MA/SF.

Generalized additive models, generalized Poisson regression models, and Cox proportional hazards models were adjusted for age, baseline visual acuity, and whether adequate loading was received (three injections within 3 months) as fixed effects, and intrapatient correlation nested within practitioners as random effects. This nesting structure helps to account for correlation of outcomes due to variations in treatment decisions, local health systems, unrecorded patient demographics, and grading of lesion activity within practitioners.

Multistate Markov modeling was used to model the transition between lesion activity states over time and estimate the proportion of eyes and average time spent in each of the lesion activity states. These models also account for the arbitrary sampling times in which the exact time of transition is generally not observed,[15,16] e.g., a patient scheduled to return after 8 weeks may be inactive for the first 6 weeks but transition to one of the active states in the last 2 weeks. In addition to the three possible activity statuses (inactive, A-NSRFL only, and A-SRFL only), an "absorbing" state was defined as either a formal discontinuation recorded by the treating physician or if it had been at least 6 months since the last observed visit. Kaplan–Meier survival curves were also used to analyze time to patient dropout between activity groups.
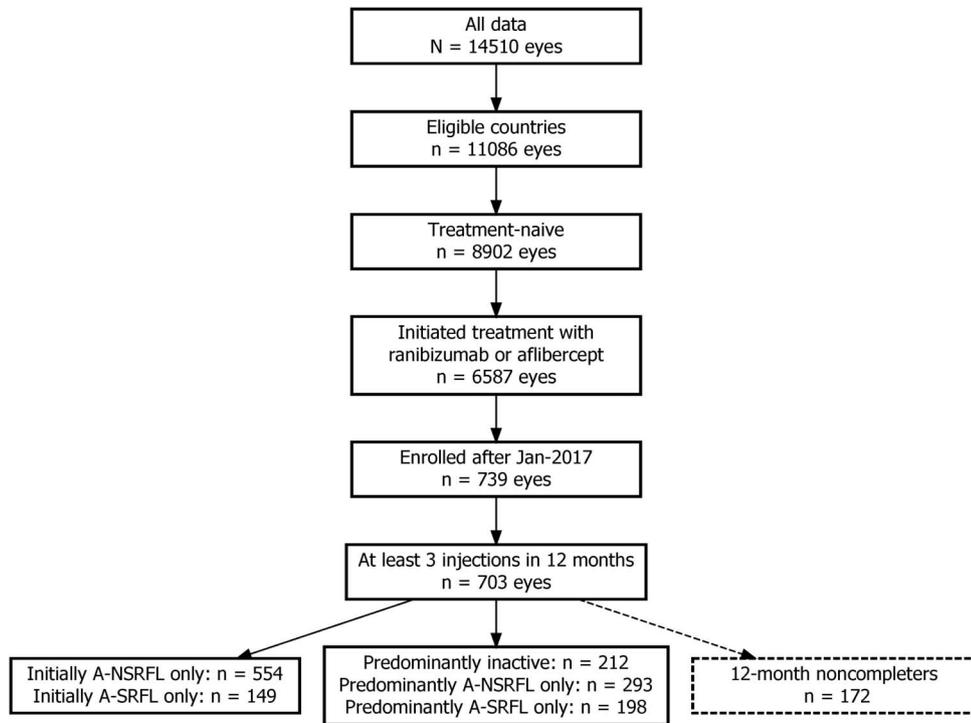
P values from pairwise comparisons were adjusted for using the Holm–Bonferroni correction. A *P* value <0.05 was considered statistically significant. Analyses were conducted in R software version 3.6.2 (R Project, The R Foundation for Statistical Computing, Vienna, Austria).[17] We used the *mgcv* package (version 1.8–31) for generalized additive models, the *glmmTMB* package (version 0.2.3) for general Poisson regression models, the *survival* package (version 3.1–8) for Kaplan–Meier analysis, the *coxme* package (version 2.2–16) for Cox proportional hazards models, and the *msm* package (version 1.6.8) for multistate Markov analysis.[15,16,18–21]

Results

Study Population

We identified 703 eyes from 619 patients that were eligible for the present analysis (Figure 1). Of these, 554 eyes were *initially A-NSRFL only* and 149 eyes were *initially A-SRFL only*. There were 212 eyes that were *mostly inactive*, 293 eyes that were *mostly A-NSRFL only*, and 198 eyes that were *mostly A-SRFL only* based on their predominant activity status throughout the 12-month follow-up period. Demographic characteristics of these patients are summarized in Table 1.

Eyes that were *initially A-NSRFL only* had significantly worse mean (SD) baseline visual acuity (56.6 [20.9] letters) than those that were *initially A-SRFL only* (63.4 [18.6] letters; *P* < 0.001). Eyes that were *mostly A-NSRFL only* had significantly worse mean (SD) baseline visual acuity (54.5 [22.1] letters) than

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┌─────────────────────────┐
│       All data          │
│     N = 14510 eyes      │
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│   Eligible countries    │
│     n = 11086 eyes      │
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│    Treatment-naive      │
│     n = 8902 eyes       │
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│  Initiated treatment with│
│ ranibizumab or aflibercept│
│     n = 6587 eyes       │
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│  Enrolled after Jan-2017│
│     n = 739 eyes        │
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│At least 3 injections in 12 months│
│     n = 703 eyes        │
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Initially A-NSRFL only: n = 554
Initially A-SRFL only: n = 149

Predominantly inactive: n = 212
Predominantly A-NSRFL only: n = 293
Predominantly A-SRFL only: n = 198

12-month noncompleters
n = 172

Fig. 1. Flowchart showing the number of eyes in the Fight Retinal Blindness! registry and inclusion criteria in the analysis.

those that were *mostly inactive* (61.4 [17.8] letters; P = 0.001) and *mostly A-SRFL only* (59.7 [20.3] letters; P = 0.010). This trend was also observed when activity groups used only visits during the maintenance phase but it was not statistically significant (see **Table, Supplemental Digital Content 1**, http://links.lww.com/IAE/B369, which summarizes demographics for activity groups based only on the maintenance phase).

Initial Activity

Adjusted 12-month visual gains were slightly higher for eyes that were *initially A-SRFL only* than for eyes that were *initially A-NSRFL only* (6.9 [4.5, 9.2] vs. 5.7 [4.5, 6.9] letters, respectively), although there was no significant difference in the longitudinal trend between the 2 groups (P = 0.165; Figure 2). However, because of differences in baseline vision, the unadjusted 12-month

mean visual acuity (SD) for eyes that were *initially A-NSRFL only* was worse than *initially A-SRFL only* eyes (62.5 [20.4] vs. 67.5 [17.9] letters; P = 0.003; Table 2).

The median (Q1 and Q3) number of injections and visits between the 2 initially active subgroups was similar (8 [6, 9] vs. 8 [6, 10] injections; P = 0.825, and 8 [7, 10] vs. 10 [8, 12] visits; P = 0.622, for *initially A-NSRFL only* and *initially A-SRFL only*, respectively).

Predominant Activity Status

There was a difference in visual outcomes over 12 months across the 3 predominant activity groups (P = 0.005), with *mostly inactive* eyes (95% confidence interval [CI]) (7.6 [5.7, 9.6] letters) and *mostly A-SRFL only* (7.5 [5.6, 9.4] letters) gaining the most mean visual acuity at 12 months and *mostly A-NSRFL only* performing the worst (3.6 [1.9, 5.3] letters) after multivariable adjustment (Figure 3A). The comparatively worse visual

Table 1. Demographic and Clinical Characteristics at Baseline With *P* Values Comparing Subgroups Based on Initial Activity and Predominant Activity Status

		Initial Activity			Predominant Activity Status			
	All Eyes	A-NSRFL Only	A-SRFL Only	*P*	Inactive	A-NSRFL Only	A-SRFL Only	*P*
Eyes	703	554	149		212	293	198	
Patients	619	498	135		194	269	182	
Gender, % female	64.5	64.1	66.7	0.582	64.9	67.7	61	0.310
Age, mean (SD)	80.3 (9.3)	80.6 (9.2)	79.2 (9.4)	0.095	81.3 (8.5)	80.4 (9.9)	79.2 (9)	0.068

Fig. 2. Predictions from longitudinal generalized additive models adjusted for baseline visual acuity and baseline age comparing initially A-NSRFL versus initially A-SRFL (*P* = 0.165). The 95% CIs for the difference in predicted visual acuity change between subgroups in (**B**) is highlighted in gray.
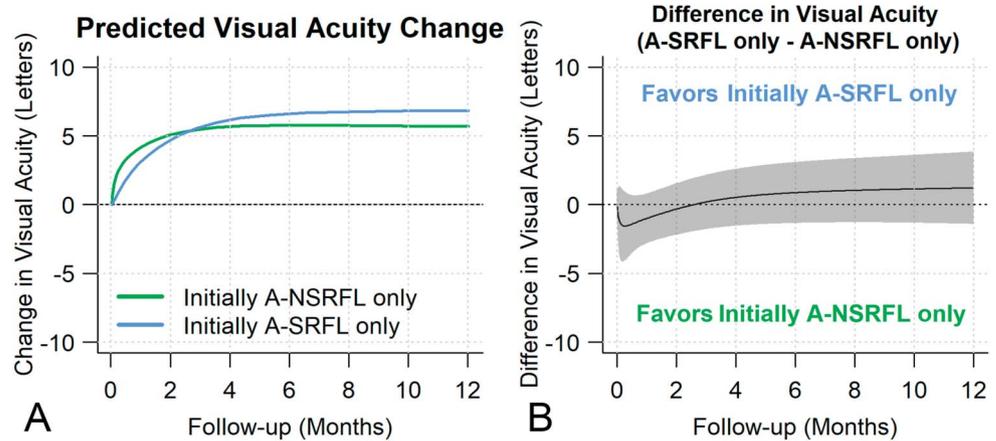
outcomes in the *mostly A-NSRFL only* eyes was more pronounced after the first 3 months because of their continuing downward trajectory after their initial gain in vision (Figure 3, B and C). These trends persisted when activity groups were based on visits during the maintenance phase alone (*P* < 0.001; see **Table, Supplemental Digital Content 2**, http://links.lww.com/IAE/B370, and **Figure, Supplemental Digital Content 3**, http://links.lww.com/IAE/B371, which summarizes visual outcomes over 12 months for

activity groups based only on the maintenance phase).

The raw median number (Q1 and Q3) of injections received was 8 (7, 9), 7 (6, 9), and 8 (7, 11) for *mostly inactive*, *mostly A-NSRFL only*, and *mostly A-SRFL only*, respectively. Multivariable adjusted models suggested there was a difference in injection frequency between activity groups (*P* = 0.003) with *mostly A-SRFL only* eyes receiving more injections than *mostly inactive* (*P* = 0.003) and *mostly A-NSRFL only* eyes (*P* = 0.022). The

Table 2. Twelve-Month Outcomes and *P* values Comparing Subgroups Based on Initial Activity and Predominant Activity Status

	Initial Activity			Predominant Activity Status			
	A-NSRFL Only	A-SRFL Only	*P*	Inactive	A-NSRFL Only	A-SRFL Only	*P*
Eyes	554	149		212	293	198	
Patients	498	135		194	269	182	
Baseline visual acuity, mean (SD)	56.6 (20.9)	63.4 (18.6)	<**0.001**	61.4 (17.8)	54.5 (22.1)	59.7 (20.3)	<**0.001***
Final visual acuity, mean (SD)†	62.5 (20.4)	67.5 (17.9)	**0.003**	67.4 (16.9)	59.2 (22.0)	65.7 (18.9)	<**0.001‡**
Unadjusted visual acuity change, mean (95% CI)†	5.9 (4.4, 7.3)	4.1 (2.1, 6.1)	0.158	6.1 (4.2, 7.9)	4.8 (2.5, 7)	6.0 (4, 7.9)	0.610
Adjusted visual acuity change, mean (95% CI)§	5.7 (4.5, 6.9)	6.9 (4.5, 9.2)	0.165	7.6 (5.7, 9.6)	3.6 (1.9, 5.3)	7.5 (5.6, 9.4)	**0.005**
Visual acuity ≤ 35 letters, % baseline/final†	16.6%/ 11.7%	9.4%/6%	0.063	10.8%/ 8.5%	19.1%/14%	13.6%/ 7.6%	**0.039¶**
Visual acuity ≥ 70 letters, % baseline/final†	35%/51.8%	45.6%/ 63.1%	**0.018**	42.9%/ 63.7%	29.7%/ 45.7%	42.4%/ 56.6%	<**0.001****
Injections, median (Q1 and Q3)††	8 (6, 9)	8 (6, 10)	0.825	8 (7, 9)	7 (6, 9)	8 (7, 11)	**0.003‡‡**
Visits, median (Q1, Q3)††	8 (7, 10)	10 (8, 12)	0.622	8 (7, 10)	8 (7, 10)	10 (8, 12)	<**0.001§§**

Significant *P* values are highlighted in bold.
*Inactive versus A-NSRFL only (*P* = 0.001); inactive versus A-SRFL only (*P* = 0.417); and A-NSRFL only versus A-SRFL only (*P* = 0.010).
†Last observation carried forward used for noncompleters, *P* values comparing final visual acuity.
‡Inactive versus A-NSRFL only (*P* < 0.001); inactive versus A-SRFL only (*P* = 0.382); and A-NSRFL only versus A-SRFL only (*P* = 0.001).
§*P* value and adjusted visual acuity change based on longitudinal generalized additive models.
¶Inactive versus A-NSRFL only (*P* = 0.157); inactive versus A-SRFL only (*P* = 0.874); and A-NSRFL only versus A-SRFL only (*P* = 0.121).
**Inactive versus A-NSRFL only (*P* < 0.001); inactive versus A-SRFL only (*P* = 0.171); and A-NSRFL only versus A-SRFL only (*P* = 0.047).
††Twelve-month completers only pairwise comparisons with Holm–Bonferroni adjustment for multiple comparisons.
‡‡Inactive versus A-NSRFL only (*P* = 0.293); inactive versus A-SRFL only (*P* = 0.003); and A-NRSFL only versus A-SRFL only (*P* = 0.022).
§§Inactive versus A-NSRFL only (*P* < 0.001); inactive versus A-SRFL only (*P* < 0.001); and A-NSRFL only versus A-SRFL only (*P* = 0.109).
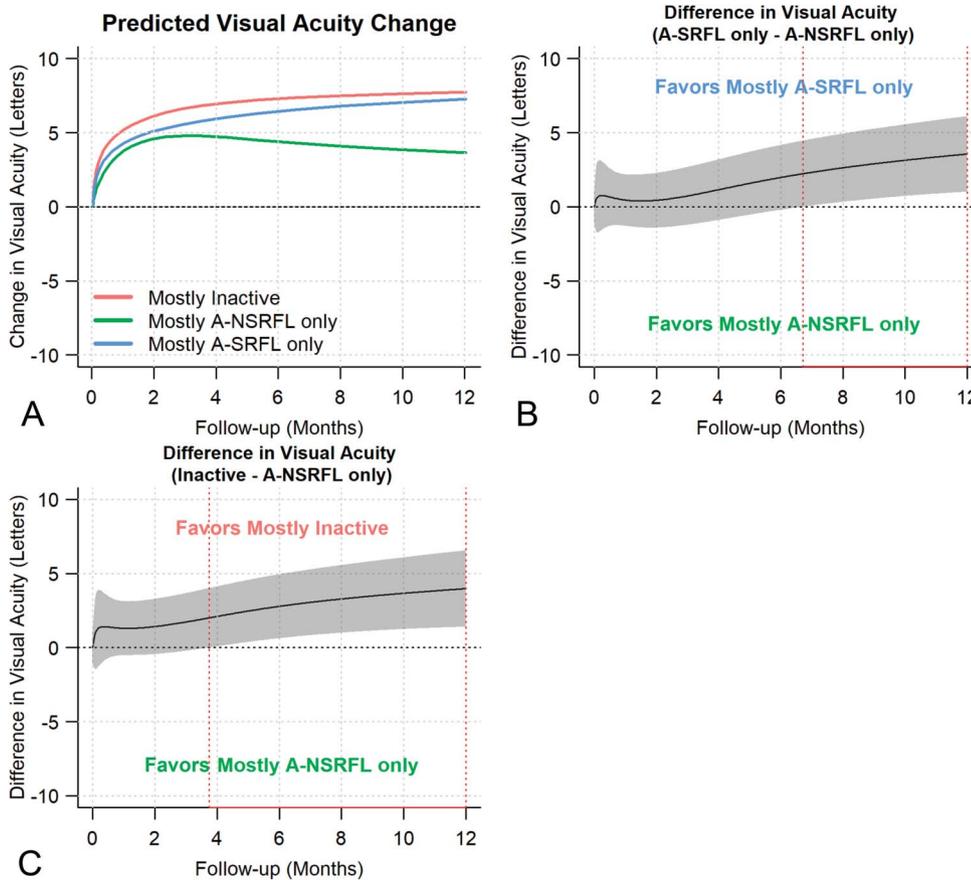
Fig. 3. Predictions from longitudinal generalized additive models adjusted for baseline visual acuity and baseline age comparing eyes that were mostly inactive, mostly A-NSRFL and mostly A-SRFL during their follow-up (global P = 0.005). The red dotted lines in (**B** and **C**) indicate periods in which the 95% CI (highlighted gray) for the difference in predicted visual acuity change between subgroups no longer crosses zero.

median number of visits was 8 (7, 10), 8 (7, 10), and 10 (8, 12) for *mostly inactive*, *mostly A-NSRFL only*, and *mostly A-SRFL only*, respectively (P < 0.001), with *mostly A-NSRFL only* and *mostly A-SRFL only* having significantly more visits than mostly inactive eyes (both P < 0.001).

Macular Atrophy and Subretinal Fibrosis

Odds ratios for the development of new MA and SF are summarized in Table 3 (see **Figure, Supplemental Digital Content 4**, http://links.lww.com/IAE/B372, which illustrates Kaplan–Meier survival curves for time to development of MA and SF).

Table 3. Hazards Ratios (95% CIs) From Mixed Effects Cox Proportional Hazards Models for the Development of Macular Atrophy or Subretinal Fibrosis Over the 12-Month Follow-Up Period

	Macular Atrophy	P	Subretinal Fibrosis	P
Initial activity		0.100		0.070
A-NSRFL only	1		1	
A-SRFL only	0.55 (0.27, 1.13)		0.40 (0.15, 1.08)	
Predominant activity				
Inactive	1	**0.003***	1	0.785
A-NSRFL only	0.47 (0.25, 0.88)		1.23 (0.57, 2.64)	
A-SRFL only	0.31 (0.15, 0.63)		1.02 (0.44, 2.37)	
Predominant activity (maintenance)				
Inactive	1	<**0.001**†	1	0.423
A-NSRFL only	0.34 (0.17, 0.68)		1.05 (0.50, 2.21)	
A-SRFL only	0.22 (0.11, 0.43)		1.49 (0.72, 3.09)	

Eyes who had atrophy or fibrosis at baseline were excluded from this analysis. A hazards ratio of one indicates the reference group. Significant P values are highlighted in bold.
Pairwise comparisons with Holm–Bonferroni adjustment for multiple comparisons.
*Inactive versus A-NSRFL only (P = 0.036); inactive versus A-SRFL only (P = 0.003); and A-NSRFL only versus A-SRFL only (P = 0.249).
†Inactive versus A-NSRFL only (P = 0.005); inactive versus A-SRFL only (P < 0.001); and A-NSRFL only versus A-SRFL only (P = 0.285).

The estimated percentage (95% CI) of eyes developing new MA was 16% (13, 20) and 11% (5, 17) for eyes that were *initially A-NSRFL only* and *initially A-SRFL only*, respectively. Eyes that were *initially A-SRFL only* were less likely to develop MA, although this was not significant (OR [95% CI]: 0.55 [0.27, 1.13]; *P* = 0.100).

The estimated percentage (95% CI) of eyes developing new MA grouped by predominant activity status was 21% (14, 27), 13% (9, 18), and 13% (7, 18) for eyes that were *mostly inactive*, *mostly A-NSRFL only,* and *mostly A-SRFL only*, respectively. Eyes that were *mostly A-NSRFL only* or *mostly A-SRFL only* were significantly less likely to develop MA than eyes that were *mostly inactive* (odds ratio [OR] [95% CI]: 0.47 [0.25, 0.88] and 0.31 [0.15, 0.63], respectively). This result was consistent when only visits during the maintenance phase were included.

The estimated percentage (95% CI) of eyes developing new SF was 16% (13, 20) and 5% (1, 9) for eyes that were *initially A-NSRFL only* and *initially A-SRFL only*, respectively. Eyes that were *initially A-SRFL only* were less likely to develop SF; however, as with MA, this was not statistically significant (OR [95% CI]: 0.40 [0.15, 1.08]; *P* = 0.070).

The estimated percentage (95% CI) of eyes developing new SF was 9% (4, 13), 19% (13, 24), and 13% (8, 19) for eyes that were *mostly inactive*, *mostly A-NSRFL only,* and *mostly A-SRFL only*, respectively. We did not find any statistically significant difference in the odds of developing SF between the predominant activity subgroups.

Activity Status Over Time

The estimated proportion of eyes in each activity state as estimated from the Markov model is illustrated in **Supplemental Digital Content 5** (see **Figure**, http://links.lww.com/IAE/B373). The proportion of eyes in which the choroidal neovascular lesion was inactive increased progressively from 0 to 4 months and remained steady at approximately 40% (38% at 12 months). By contrast, the proportion of eyes that were A-NSRFL only decreased from 0 to 4 months and remained at approximately 20% thereafter (21% at 12 months). The proportion of eyes that were A-SRFL only remained at approximately 20% throughout the 12-month follow-up period (17% at 12 months). The rate of discontinuation at 12 months was 24%.

Discussion

This analysis suggests that the distribution of fluid at baseline and during treatment affects the 12-month visual outcomes of eyes treated for nAMD in routine clinical practice. Eyes that were *mostly A-SRFL only* achieved similar 12-month visual outcomes to those that were *mostly inactive*, and both groups outperformed eyes that were *mostly A-NSRFL only*. Thus, our results provide further evidence that tolerating SRFL is compatible with good visual outcomes, at least in the short term.

The 24-month FLUID randomized clinical trial reported that eyes in which SRFL was tolerated had comparable visual outcomes to those in which it was not (mean improvement: +2.6 letters vs. +3.0 letters) with fewer injections.[4] We also found good visual outcomes in the *mostly A-SRFL only* group. However, this group may have received somewhat more treatments and visits than the *mostly inactive* and *mostly A-NSRFL only* groups. This may be because practitioners continued to treat patients with persistent SRFL at 4-week intervals before deciding to tolerate the fluid, if they ever did. The *mostly A-NSRFL only* group received fewer injections than the *mostly inactive* (nonsignificant) and the *mostly A-NSRFL* eyes (significant). This could be a sign of undertreatment relative to the patient's needs based on activity levels or ineffective treatment extensions under a treat-and-extend regimen. Better results may have been observed with more injections in this group. Regardless, it highlights the lack of tolerance and need to injection of nonsubretinal fluid are present.

There is a growing body of evidence on the relationship between fluid and the development of MA. Baseline IRFL has been reported to be associated with higher rates of macular atrophy, whereas baseline SRFL was associated with less atrophy at 2 and 5 years in the CATT study.[5,22,23] We also found a lower risk of developing MA in the group with baseline SRFL only, although it was not statistically significant (OR: 0.55 for A-SRFL only vs. A-NSRFL only; *P* = 0.100). When we considered predominant lesion activity throughout the follow-up period, we found that the presence of not only SRFL only but also IRFL was associated with a reduced risk of macular atrophy during the first year of treatment. An earlier report from the same database similarly found a higher proportion of visits in which the lesion that was graded as inactive was the strongest risk factor for the development of macular atrophy.[8] Whether eyes with IRFL that persists for >1 year will continue to have a lower risk of MA remains to be seen.

It has been suggested that baseline SRFL may be a risk factor for the development of subretinal fibrosis.[24,25] We found SRFL at baseline was associated with a lower risk of developing subretinal fibrosis, although this effect was not statistically significant

(OR: 0.40 for A-SRFL only vs. A-NSRFL only; P = 0.070). An earlier analysis of the same database found that a higher proportion of visits with active lesion were associated with an increased risk of subretinal fibrosis over a 10-year period.[12] However, the grading of lesion activity did not distinguish between IRFL and SRFL. This study found no significant association between fluid and subretinal fibrosis, regardless of whether it was IRFL or SRFL. A longer-term study may establish whether the type of fluid is associated with the development of subretinal fibrosis.

There are some limitations that we would like to acknowledge. Treatment decisions, including drug choice, treatment regimen, and retreatment criteria were at the discretion of the physician and thus based entirely on the clinician's own judgment. The A-NSRFL only activity grading did not allow for the distinction between activity with IRFL only, IRFL and SRFL, hemorrhage alone, or any combination of these excluding SRFL only. However, the distinction between IRFL alone and with SRFL was determined to be less important because in SRFL only the presence of any IRFL is likely to require treatment, and hemorrhage without IRFL, although possible, is uncommon and treated in the same way as IRFL. The 12-month noncompletion rate of 24% was high, but typical of observational studies. Reasons for discontinuation were not recorded in most cases—we have previously reported that most people who are lost to follow-up in our database because of causes unrelated to poor outcomes, such as patient death or going to another doctor, although some do drop out because of poor outcomes.[26–28] Including noncompleters in our analysis using longitudinal mixed models is an appropriate method to deal with dropouts provided the data are missing at random.[29] The assumption of missing at random is reasonable provided that the 12-month outcomes for noncompleters can be reasonably inferred based on their visual acuity measurements leading up to dropout and they did not experience any unobserved deviations from their observed trajectory. Grading of MA and SF was unable to be verified by a reading center. This reflects routine clinical practice because reading centers are generally not available, and the presence of atrophy or fibrosis is left to the clinical expertise of the physician. We have previously reported that the presence or absence of atrophy in a sample of the FRB! database was accurate in approximately 80% of cases.[8] There may also be differences in the definition of atrophy and fibrosis and imaging techniques, both across studies and between doctors participating in the FRB! registry.[5,8,12,30] We have attempted to account for intradoctor variation in our statistical models; however, there will still be difficul-ties when comparing our results with previously published research.

In conclusion, our data suggest that eyes that were predominantly active with SRFL only had similar visual outcomes at 1 year to eyes that were predominantly inactive. The presence of IRFL, on the other hand, was associated with worse visual outcomes, highlighting the importance of distinguishing between IRFL and SRFL when managing treatment for nAMD.

Key words: intraretinal fluid, neovascular age-related macular degeneration, subretinal fluid.

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