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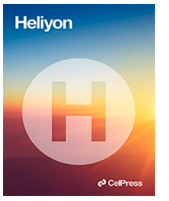

Research article

Dynamics and patterns of recurrence in neovascular AMD during real-world management using automated fluid monitoring☆

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A B S T R A C T

In this retrospective longitudinal observational study, data from one site of the Fight Retinal Blindness! Registry (University of Zurich, Switzerland) was used to investigate the quantity and distribution of recurrent fluid in neovascular age-related macular degeneration (nAMD). Study eye eligibility required treatment-naïve nAMD, receiving at least three anti-vascular endothelial growth factor injections, followed by a treatment discontinuation of at least six months and subsequence fluid recurrence. To quantify fluid, a regulatory approved deep learning algorithm (Vienna Fluid Monitor, RetInSight, Vienna, Austria) was used. Fifty-six eyes of 56 patients with a mean age of 76.29 ± 6.58 years at baseline fulfilled the inclusion criteria. From baseline to the end of the first treatment-free interval, SRF volume had decreased significantly (58.0 nl (IQR 10–257 nl) to 8.73 nl (IQR 1–100 nl), $p < 0.01$). The quantitative increase in IRF volume from baseline to the end of the first treatment-free interval was not statistically significant (1.35 nl (IQR 0–107 nl) to 5.18 nl (IQR 0–24 nl), $p = 0.13$). PED also did not reach statistical significance ($p = 0.71$). At the end of the second treatment discontinuation there was quantitatively more IRF (17.3 nl) than SRF (3.74 nl). In conclusion, discontinuation of treatment with anti-VEGF therapy may change the fluid pattern in nAMD.

1. Introduction

Long-term treatment of neovascular age-related macular degeneration (nAMD) in real-world is time-consuming and a financial burden for healthcare providers. Different treatment regimens with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections have been developed, including fixed monthly or bimonthly, pro-re-nata, treat-and-extend and subretinal fluid (SRF)-tolerant regimen [1]. The cause for the multiplicity of regimen lies in diverse disease conditions and even though biomarkers for visual prognosis have been suggested [2], regular examinations are obligatory to keep the disease under control [3]. Commonly, when the macular neovascular membrane (MNV) activity is resolved, treatment intervals are extended, but no reliable predictors or biomarkers are known when and in which presentation to expect recurrence of MNV activity.

To create personalized treatment strategies and to evaluate disease activity precisely, artificial intelligence algorithms (AI) were developed. These algorithms identify retinal fluid by compartment in a volumetric scan and calculate fluid volumes in nanoliters (nl). An AI-supported fluid quantification in each compartment provides a precise documentation of disease progression, therewith

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individual treatment regimen can be established. It is intuitive that AI-supported observations and treatment decisions may be more objective and robust than subjective qualitative assessments, enabling targeted treatment.

In nAMD, SRF, intraretinal fluid (IRF) and especially fluid fluctuations are signs of disease activity, which progressively lead to long-term visual function loss [4]. Furthermore, different types of macular neovascularization have different manifestations in terms of fluid distribution, disease progression and treatment [5,6]. For example, type I MNV leads less frequently to macular atrophy in comparison to type II and III lesions. Type III is well known for IRF and intraretinal spot hemorrhages [7]. Whilst 100 % of type III lesions showed a cystoid edema in the study of Ravera et al. only 14 % of other MNV types featured cystoid fluid [8]. Furthermore, visual prognosis is MNV type dependent [9]. Therefore, when investigating progression and patterns of nAMD, exact location of fluid as well as MNV types should be considered.

Extensive studies have been conducted observing nAMD cohorts treated with different anti-VEGF agents as well as using different treatment regimen over time. Number of administered treatments and duration of treatment-free intervals were reported. However, no analyses have focused on the patterns of disease recurrence following treatment discontinuation. This study was conducted to gain better understanding of how neovascular activity and therefore fluid recurrence changes after treatment discontinuation. This insight leads to a better understanding of the impact of treatment discontinuation on disease outcomes and could help to develop individualized treatment regimes.

2. Methods

This investigation was a post-hoc analysis, evaluating a prospectively designed, observational database of eyes with nAMD. These eyes were observed from the first, treatment-naïve presentation onwards throughout long-term intravitreal therapy of anti-VEGF (aflibercept or ranibizumab) in routine clinical practice [10]. This study was approved by Medical University of Vienna ethics committee (1246/2016) and adhered to the tenets of the Declaration of Helsinki. It is an anonymized post hoc analysis of the real world data from Fight Retinal Blindness! Registry (FRB!) registry images of one site (Zürich, Switzerland). Informed consent was obtained from all participants.

Inclusion criteria were eyes diagnosed with treatment-naïve nAMD, at least three received anti-VEGF injections within the first six months of treatment, followed by a treatment-free interval of at least six months and fluid recurrence afterwards. At this site of the FRB! registry, the regime treat and extend was conducted in a real world setting. Treatment was discontinued for medical reasons (e.g. no disease activity or change in visual acuity) after the maximum extension of the time interval used in the treat-and-extend regimen (16 weeks) or for patient-related reasons. This also means that treatment interruptions could have been made earlier than waiting for the required 16-week interval without MNV activity. The time period of treatment before treatment discontinuation was not restricted. Exclusion criteria were missing data of the treatment-naïve state, macular fibrosis or macular atrophy at baseline, total follow-up of less than one year and any macular disease that could affect visual acuity (e.g. full thickness macular hole, vitreomacular traction). The inclusion criteria and number of included and excluded eyes is further described in Fig. 1.

To ensure the quality of the results, the fovea was annotated manually for each Optical Coherence Tomography (OCT) volume-scan. A total of 213 OCTs were analyzed, including an OCT of the treatment-naïve state and each start and end of treatment discontinuation. In order to quantify retinal fluid, a deep learning algorithm was used (Vienna Fluid Monitor, RetInSight, Vienna, Austria) which has received regulatory approval in Europe. The algorithm measured fluid volume separately in each compartment (IRF, SRF, PED) in each

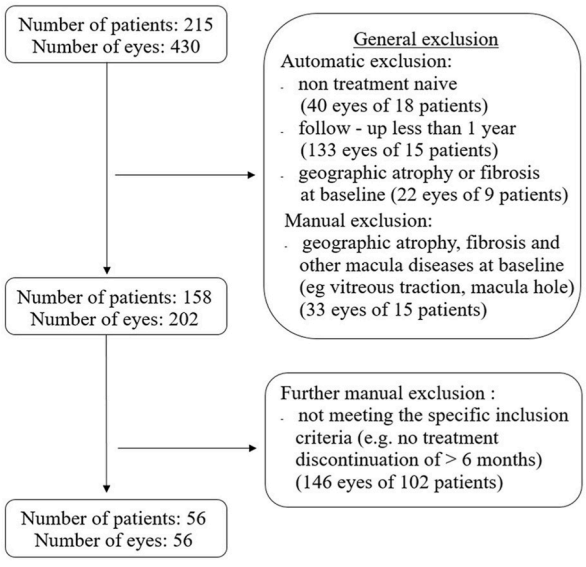

Fig. 1. Shows the automatic and manual patient's exclusion criteria.

B scan within the central 6 mm. The certified algorithm (EU 2017/745) that was used showed outstanding accuracy for detection of SRF and IRF and achieves a high level of agreement with manual expert assessment [11–13].

Additional analysis was performed with eyes that showed more than one treatment-free interval. For further evaluation, MNV types were determined at baseline (type I, II, mixed (type I and II) and III) based on the OCT image. If the MNV type was not clearly identifiable, it was graded as 'not gradable' and excluded from the subgroup analysis. Subgroup analysis was performed separately according to the MNV type.

Appropriate descriptive statistics (mean and SD if normally distributed as well as median and interquartile range (IQR) if not normally distributed) were computed. A Wilcoxon Signed Rank test was performed, as macular fluid volumes are usually not normally distributed. The proportions of each fluid compartment with respect to the total fluid in each OCT volume was calculated in percentages. A Hurdle-Gamma generalized linear mixed model (glmm) was fitted to account for zero excess of all three fluid variables using the statistical computing software R and its package glmm TMB [14].

3. Results

3.1. Retreatment frequency and timing of treatment-free intervals

Fifty-six eyes of 56 patients met the inclusion criteria. The mean age at baseline was 76.29 ± 6.58 years. Sixteen (IQR 6.00–27.75) months of treatment were performed to reach a treatment-free interval of at least six months. 56 eyes with at least one treatment discontinuation were analyzed for fluid evaluation. In 18 eyes, a second discontinuation of at least six months was observed. In five eyes, even more than two discontinuations of at least six months were noted. The mean number of visits during the treatment breaks was 6.9 (0–20) for the first break and 4.9 (0–18) for the second break. The median overall observation time was 70.5 months (IQR 50.25–90.25 months).

A minimum of 4 and a maximum of 66 injections with a median of 25 (IQR 13–35.25) injections were received during the observed follow-up period. To enable the first treatment discontinuation of at least six months, a median of 12.66 (IQR 5–16) injections had been received. A median of one injection (IQR 1–4.5) has been given between the end of the first and start of the second intermission. Visual acuity increased after the initial treatment phase (0.57 ± 0.49 logMar at baseline and 0.48 ± 0.46 logMar at start of the discontinuation) and slightly decreased at the end of the treatment-free interval to 0.48 ± 0.47 logMar. Using the best visual acuity of each patient, the best mean visual acuity was 0.39 ± 0.43 logMar. The best visual acuity was achieved at the treatment naïve state in 12 eyes, at the start of a treatment discontinuation in 25 eyes and at the end of a treatment discontinuation in 19 eyes. In 57 % (32 eyes), the highest visual acuity coincided with the lowest amount of retinal fluid in the central millimeter (IRF and SRF).

Details of both groups with either at least one or at least two discontinuations are given in Table 1.

Table 2 describes the median fluid volumes and the percentages of IRF, SRF and PED as proportions of the total fluid volume of the entire cohort. The central 6 mm disc was used for all fluid measurements. Fig. 2 shows fluid distribution at each investigated time point.

3.2. Type and amount of fluid recurrence

At baseline, IRF volumes were low and SRF volumes were high, and PED volumes of more than 200 nl were seen in 39 % of all patients. Treatment was discontinued by the clinician when IRF has completely and SRF substantially resolved or due to personal reasons of the patient (two patients showed more than 10 nl IRF). When recurrent fluid necessitated that treatment was resumed IRF had largely increased to levels above baseline, while SRF had increased in comparison to the start of treatment discontinuation but was much less compared to baseline values. This characteristic pattern was seen again and even more enhanced during the subsequent treatment discontinuation with remarkable increases in IRF, yet little increase in SRF was noted.

Regarding switching between IRF and SRF, of all eyes, that showed more SRF than IRF at baseline, 83.8 % also presented more SRF than IRF at the end of the first treatment-free intervals. On the other hand, of all patients, who showed more IRF than SRF at baseline, only 51.9 % also had more IRF than SRF at the end of the first intermission.

The Wilcoxon Rank test showed that SRF fluid volumes changed significantly from baseline to the end of the first discontinuation

Table 1
Shows the median time period from baseline to each investigated time point, the number of injections and the visual acuity at each investigated time point. BCVA = best corrected visual acuity, BSL = baseline, IQR = interquartile range.

	Months to BSL		Injections		BCVA (logMAR)	
	Median	*IQR (25%-75 %)*	Median	*IQR (25%-75 %)*	Mean	SD
BSL (n = 56)	na		0	0	0.57	0.49
Start first discontinuation (n = 56)	16	22 (6.00–27.25)	10.5	11 (6.00–17.00)	0.48	0.46
End first discontinuation (n = 56)	27	23 (18.50–39.50)	10.5	11 (6.00–17.00)	0.48	0.47
BSL (n = 18)	na		0	0	0.67	0.49
Start first discontinuation (n = 18)	12.5	20 (5.50–25.50)	9	10 (5.75–18.25)	0.48	0.43
End first discontinuation (n = 18)	22.5	16 (15.75–31.75)	9	10 (5.75–18.25)	0.53	0.49
Start second discontinuation (n = 18)	27.5	34 (19.75–53.50)	12.5	17 (9.50–26.75)	0.54	0.52
End second discontinuation (n = 18)	40.5	34 (33.00–67.25)	12.5	17 (9.50–26.75)	0.62	0.55

Table 2
Shows median fluid volumes and the percentages of IRF, SRF and PED as proportions of the total fluid volume of the entire cohort at each time point in the central 6 mm. BSL = baseline, IRF = intraretinal fluid, nl = nanoliter, SRF = subretinal fluid, PED = pigment epithelium detachment.

	IRF		SRF		PED	
	nl (IQR)	%	nl (IQR)	%	Nl (IQR)	%
BSL	1.35 (0–107.15)	20 %	58.0 (9.93–256.86)	52 %	0 (0–555.4)	28 %
Start first discontinuation (n=56)	0 (0–2.03)	14 %	1.6 (0.15–7.64)	54 %	0 (0–390.30)	32 %
End first discontinuation (n=56)	5.18 (0–24.36)	27 %	8.73 (0.83–100.19)	43 %	0 (0–548.9)	30.86 %
Start second discontinuation (n=18)	1.38 (0.06–9.56)	31 %	0.53 (0.15–1.56)	43 %	0 (0–512.1)	27 %
End second discontinuation (n=18)	17.30 (0.24–90.69)	30 %	3.74 (0.34–26.68)	41 %	0 (0–700.3)	29 %

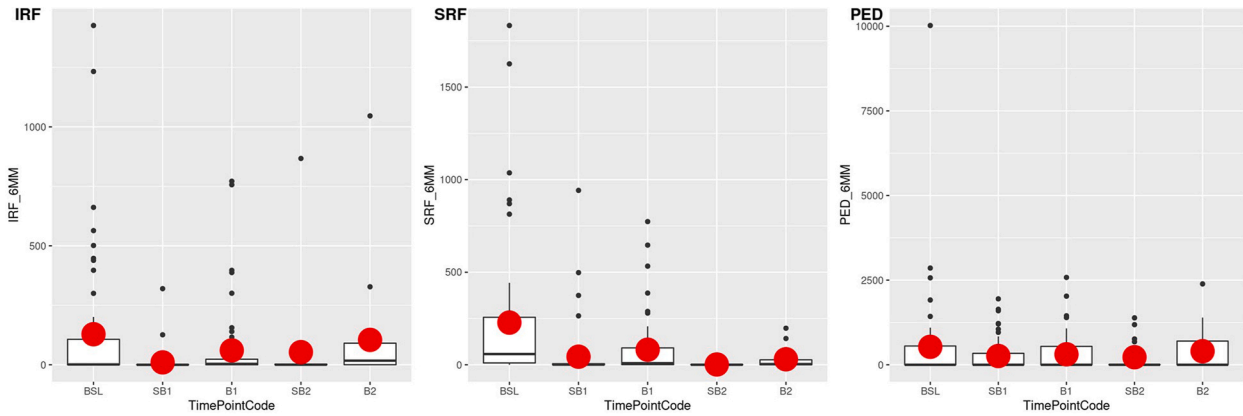

Fig. 2. Shows fluid distribution at each time point; absolute values of IRF at baseline, start of the first discontinuation (SB1), end of first discontinuation (B1), start of second discontinuation (SB2), end of second discontinuation (B2) are shown in the left boxplot, absolute values of SRF in the middle boxplot and absolute values of PED in the right boxplot. The mean values are indicated by red dots.

($p < 0.001$), IRF fluid volumes showed a trend, even though not statistically significant ($p = 0.11$) and PED fluid volumes did not change significantly ($p = 0.40$). All proportion tests are not significant, although SRF and IRF might be significant in a larger cohort ($p = 0.06$ for SRF, $p = 0.09$ for IRF, $p = 0.55$ for PED).

A Hurdle-Gamma generalized linear mixed model (glmm) was fitted to account for the zero excess of all three fluid variables. The glmm results show that there is a significant difference between baseline and end of first discontinuation ($p < 0.01$) and baseline and end of second discontinuation ($p < 0.01$) concerning SRF fluid volumes. According to the results of the conditional models, from baseline to the end of the first discontinuation, IRF fluid volumes were −0.80 nl, SRF -1.17 nl and PED -0.18 nl. From baseline to the end of the second discontinuation, IRF fluid volumes were −0.15 nl, SRF -2.11 nl and PED 0.32 nl.

3.3. Distribution of MNV types

Comparable with other studies [15], MNV type 1 was found in 28 eyes (50 %), type 2 in 12 eyes (21 %), mixed type in 5 eyes (9 %), type 3 in 9 eyes (16 %). In two eyes (3 %), the MNV type was not gradable. Of all eyes, that had a second treatment discontinuation of at least 6 months, MNV type 1 was found in 9 eyes (50 %), type 2 in 4 eyes (22 %), mixed type in 2 eyes (11 %), type 3 in 2 eyes (11 %). In one eye (6 %), the MNV type was uncertain. Therewith no difference between eyes with one intermission and eyes with more than one intermission relating to the MNV type was noticeable. No significant difference was found between MNV types and fluid volumes (IRF, SRF, PED) separately nor with respect to total fluid ($chi^2 = 3.14$, $p = 0.21$). Furthermore, no significant difference was found between the MNV types and days to end of first discontinuation ($chi^2 = 1.61$, $p = 0.45$).

4. Discussion

Extension of treatment intervals relieve the therapy burden for both patients and healthcare systems, from a financial and hospital management perspective. Still, macular degeneration must be monitored closely to ensure that vision is not affected in the long run. Medical care of nAMD (whether treatment or observation) is time-consuming due to the high number of patients on the one hand and on the other hand due to the arduous task of inspecting every OCT volume B-scan for signs of MNV activity. Accounting for the diverse morphologic manifestation of nAMD, long-term prediction is particularly difficult and a lot of experience is required to correctly assess disease activity. Accordingly, researchers focus on the development and optimization of deep learning algorithms as clinical decision support systems for the sake of efficiency and time-saving. Not only the automated detection of fluid in a few seconds is an impressive function of AI tools, but also assessing and predicting MNV activity and treatment requirements is of high interest. It could help to

avoid unnecessary additional appointments, over- and undertreatment [16]. Therefore, from the current state of knowledge, it is beneficial to know the time period of disease reactivation, how aggressively the fluid returns and how often therapy is needed to return to an inactive state.

The aim of this study is to identify a population of patients with known baseline condition, which qualified for an extended treatment-free interval and compare the fluid features in recurrence based on volume in different fluid compartments. Discontinuation of treatment for 6 months leaves enough time for biological and morphological changes to become apparent. The results of this study show that at baseline, a large proportion of total fluid is found in the subretinal compartment. More than one year of continuous therapy were needed on average to be able to implement a treatment-free interval of at least half a year. In comparison to the treatment naïve state, the SRF volume decreased significantly while IRF volume increased after a treatment discontinuation. The volume of PED did not change significantly. In patients for whom even two long intermissions were carried out due to MNV inactivity, the first discontinuation could be started earlier than in patients for whom only one treatment discontinuation could be carried out due to disease activity. Also, in eyes with more than one treatment-free interval, the fluid distribution again showed a decrease in the subretinal fluid volume and an increase in the intraretinal fluid volume. In this study, in contrast to other studies, the type of MNV neither influenced the quantity of fluid in each compartment, nor the total fluid [9,17,18]. This finding might be due to the small number of eyes that applied to the inclusion criteria of this investigation.

Most of the recent randomized controlled trials (RCT) focus on prolongation of retreatment intervals either by the choice of the regimen or new substance [19,20]. Invariably, only a cluster-randomized trial (CRT) is used as an indication for retreatment indication and defining the optimal interval. Systematic correlation of CRT and realistic fluid amounts demonstrated little correlation between CRT and measurement of fluid volumes in neovascular AMD [21]. Retrospective analyses demonstrate the importance of compartments on functional outcomes with IRF having a negative impact on BCVA, while SRF may be tolerated without visual loss [22,23]. Hence, not the length of the intervals, but also the compartmentalization of fluid as well as the dynamics of volume changes matter. In the Lucerne and Tenaya study the proportion of patients switching up and down to different intervals despite the use of a sophisticated personalized treatment interval (PTI) assessment was surprisingly high [19].

With rising life expectancy and advancing treatment options in AMD, support is needed to address the increasing workload. Implementation of AI such as the Fluid Monitor, is a turning point for ophthalmology in the clinical setting. Furthermore, using AI in research brings several advantages: AI guided qualitative and quantitative fluid/biomarker detection achieved a higher level of accuracy than retinal specialists [24]. The time consuming annotation takes up to 15 h per OCT volume scan for retinal specialists for a task which can be accomplished by algorithms in a fraction of time [25]. Due to imprecise and time-consuming manual analysis of OCTs, AI might help us to better monitor AMD patients.

Treatment discontinuation due to inactivity of the MNV lesions are integrated in most treatment regimes. Naturally, this must be differentiated from treatment interruption due to loss of follow-up. Reasons for discontinuation due to patients' compliance are long treatment intervals, low visual acuity at baseline and at the time of discontinuation and poor response to anti-VEGF [26]. Furthermore, the global COVID-19 pandemic led to treatment discontinuations independent of the MNV activity [27]. This study focuses on planned treatment halt due to absent MNV activity rather different from loss to follow-up in a real world setting [17,28–30].

Intraretinal fluid volumes increased with every treatment discontinuation in this study. Subretinal fluid volumes, on the other hand, decreased after a treatment-free interval in comparison to the treatment-naïve state. This trend continues with each discontinuation. More presence and volume of IRF may indicate progressing degeneration of the retina as known from IRF persisting over the loading dose which is associated with lower visual acuity at baseline and as final outcome [31]. IRF and especially persistent IRF is well known to lead to worse visual acuity [32]. Also, the risk of scar formation is increased with time of persistent IRF [33]. Therewith, in cases of present IRF, the indication for treatment is clear. With SRF, different treatment recommendations can be found in the literature. In daily routine, about half of all physicians see any SRF -just as IRF- as an indication for anti-VEGF treatment, whereas the other half tolerates some amount of SRF [2]. Several studies report the negative impact of recurrent SRF on visual acuity [34,35]. However, others recently showed that SRF does not need to be treated as aggressively as IRF and small, constant amounts of SRF can be tolerated [9,23]. Moreover, when looking at visual acuity, a decrease of IRF is consistent with better visual acuity and vice versa [34]. On the other hand, better visual prognosis is not necessarily dependent on the absence of SRF [36,37]. Also, it was observed that eyes with residual SRF tend to develop less atrophy [38]. Still, residual SRF was observed to have a consistent negative effect on visual acuity [12]. In summary, the scientific community is still trying to understand the role of SRF [23,39]. However, SRF fluctuations should be avoided [22].

In terms of MNV biology, one may hypothesize that inducing regression of a type 1 MNV which produces SRF and also nurtures the overlying RPE and photoreceptors, may lead to neurosensory retina degeneration as reflected in IRF [17]. We analyzed the different behavior of MNV type I, II, mixed and III lesions. In this study, no significant difference was found when investigating the amount of fluid to the end of a treatment discontinuation. The small number of eyes per subgroup could explain this finding. Still, the relatively small number of eyes per MNV type leads to low statistical power from Kruskal-Wallis test and needs to be investigated with a higher number of patients per subgroup.

A limitation of this study is the small sample size, justifiable by the special cohort and the - for this research question needed - long observation time. Especially when analyzing different behaviors of individual MNV types, further investigations with more eyes are needed. Due to the real-world setting, reasons for discontinuity of treatment other than no activity (e.g. the patient did not want treatment) were not excluded. Another limitation is discontinuation due to vision loss and other reasons than MNV activity reasoned by the real-world scenario. Additionally, IRF was not subdivided into exudative and degenerative fluid, which might have an influence on IRF volumes. Also, eyes with atrophy/fibrosis in the central millimeter were excluded and might behave differently.

One option how to handle nAMD is to continuously administer anti-VEGF injections, even without MNV activity. This is hardly

manageable due to the high number of patients. Also, it would lead to an unnecessary overtreatment which results in a higher treatment burden for healthcare systems and patients. The other option, underlined by the results of our study, is consistent monitoring with OCT and automated fluid quantification, both during periods of MNV activity and therewith treatment as well as in periods without treatment. Home monitoring could be a future possibility to have constant observation on the one hand and to relieve the outpatient clinics on the other hand, yet requires a complex infrastructure. In the future, AI-guided routine OCT devices could be placed in primary care offices or pharmacies where patients can receive routine OCT check-ups on a regular basis and be notified if a follow-up visit at an eye clinic is necessary. Thousands of OCT devices are currently used by non-medical eye care professionals and may well be empowered by AI-based analysis to participate in shared care [40–42]. This might help to have constant observations on the one hand and to relieve the high observation/treatment burden in outpatient clinics on the other hand. Rigorous monitoring should be encouraged during extended treatment-free intervals. Understanding the evolution of nAMD over time is crucial to optimize diagnosis and therapy and automated OCT-based tools are essential to access the pathognomonic hallmarks objectively and precisely.

In conclusion, the aim of this study was to characterize the fluid distribution in recurrence of nAMD after a treatment discontinuation of at least 6 months. We showed that if MNV activity returns, it comes back aggressively with an increasing amount of (negative) IRF and decreasing amount of (positive) SRF in comparison to the treatment naïve state.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

CRediT authorship contribution statement

Veronika Prenner: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ursula Schmidt-Erfurth:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Philipp Fuchs:** Writing – review & editing, Data curation, Conceptualization. **Oliver Leingang:** Software, Resources, Methodology, Formal analysis. **Leonard Mana Coulibaly:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Hrvoje Bogunovic:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Daniel Barthelmes:** Writing – review & editing, Data curation, Conceptualization. **Gregor Sebastian Reiter:** Writing – original draft, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Schmidt-Erfurth: Grants: Boehringer, Genentech, Heidelberg Engineering, Janssen, Kodiak, Novartis, Roche, RetInSight, Apellis Pharmaceuticals; Consulting fees: Boehringer, Heidelberg Engineering, Kodiak, Roche, Apellis Pharmaceuticals; Honoraria for lectures: Apellis, Roche; Support for attending meetings: Apellis.
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