CJO JCO

Original article

Long-term effect of fluid volumes during the maintenance phase in neovascular age-related macular degeneration in the real world: results from Fight Retinal Blindness!

Q1 Gregor S. Reiter,* Virginia Mares,*,† Oliver Leingang,* Philipp Fuchs,* Hrvoje Bogunovic,* Daniel Barthelmes,‡ Ursula Schmidt-Erfurth*

Purpose: To investigate the effect of macular fluid volumes (subretinal fluid [SRF], intraretinal fluid [IRF], and pigment epithelium detachment [PED]) after initial treatment on functional and structural outcomes in neovascular age-related macular degeneration in a real-world cohort from Fight Retinal Blindness!

Methods: Treatment-naive neovascular age-related macular degeneration patients from Fight Retinal Blindness! (Zürich, Switzerland) were included. Macular fluid on optical coherence tomography was automatically quantified using an approved artificial intelligence algorithm. Follow-up of macular fluid, number of anti–vascular endothelial growth factor treatments, effect of fluid volumes after initial treatment (high, top 25%; low, bottom 75%) on best-corrected visual acuity, and development of macular atrophy and fibrosis was investigated over 48 months.

Results: A total of 209 eyes (mean age, 78.3 years) were included. Patients with high IRF volumes after initial treatment differed by −2.6 ($p = 0.021$) and −7.4 letters ($p = 0.007$) at months 12 and 48, respectively. Eyes with high IRF received significantly more treatments (+1.6 [$p < 0.001$] and +5.3 [$p = 0.002$] at months 12 and 48, respectively). Patients with high SRF or PED had comparable best-corrected visual acuity outcomes but received significantly more treatments for SRF (+2.4 [$p < 0.001$] and +11.4 [$p < 0.001$] at months 12 and 48, respectively) and PED (+1.2 [$p = 0.001$] and +7.8 [$p < 0.001$] at months 12 and 48, respectively).

Discussion: Patients with high macular fluid after initial treatment are at risk of losing vision that may not be compensable with higher treatment frequency for IRF. Higher treatment frequency for SRF and PED may result in comparable treatment outcomes. Quantification of macular fluid in all compartments is essential to detect eyes at risk of aggressive disease.

Age-related macular degeneration (AMD) is a progressive degenerative disease that can lead to severe visual loss and consequently increase demands on health systems worldwide.[1,2] AMD is primarily a degenerative disease, but macular neovascularizations (MNV) can develop as a serious complication.[3] Although neovascular AMD (nAMD) represents a minority of AMD cases, it is responsible for most of the acute and severe vision loss.[4] Diagnosis, decision to start treatment, and retreatment decisions for patients with nAMD are mostly based on optical coherence tomography (OCT) imaging.[5] The presence of increased proangiogenic factors such as vascular endothelial growth factor (VEGF) was found to be the major cause of disease activity, and intravitreal anti-VEGF therapy became the "gold standard" of treatment.[6] Despite continuous research to develop more efficient and longer-lasting pharmacologic therapies, intravitreal anti-VEGF treatment in the real world is still lacking effectiveness in visual outcomes when compared with clinical trials.[7,8] Nonadherence or diminished treatment frequencies in the real world compared with strict protocols in clinical trials may explain these suboptimal outcomes.[7] In addition, fluid dynamics are important regarding treatment requirements and prognosis in nAMD.[9] Given these decidedly individual factors, there is an utmost need to personalize treatment regimens in nAMD.[10]

The role of artificial intelligence (AI) in personalized treatment in retinal disease is indispensable. By harnessing vast data sets, AI algorithms can identify subtle image patterns and individual treatment response that may evade human analysis. However, training and validating a new algorithm for subsequent testing can be challenging. The training process involves specialized human resources on a reliable and time-consuming image-annotation process. The validation must assess the model's ability to accurately interpret and analyze the data present in each OCT scan, comparing the AI-generated interpretations against expert human annotations.[11] Additionally, testing a model's generalization across different data sets and clinical settings helps

https://doi.org/10.1016/j.jcjo.2023.10.017
ISSN 0008-4182

to ascertain its real-world applicability.[12] Recent advances in automated deep learning algorithms used for nAMD allow for precise and reliable determination of fluid quantity and location in different retinal tissue compartments.[13,14] Intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachment (PED) have proven to be valuable biomarkers for predicting visual outcomes, treatment need, and late-stage outcomes in clinical trials and daily practice.[9,12,15] Previous studies reported that the amount of SRF was related to a higher number of injections during the first year of treatment but not directly corresponding to visual impairment. PED and mostly IRF have a stronger relation with worse visual outcomes.[9,15,16] A recent investigation showed that larger residual fluid in all 3 compartments may be associated with vision loss, even though IRF has the most negative effect.[15]

Precise fluid quantification represents an important step toward personalized medicine and more accurate treatment management in nAMD.[16,17] Compared with clinical trial data, real-world registry data are usually more generalizable and important for management in daily practice. Using automated AI fluid quantification with OCT, we aimed to investigate the effect of post−initial treatment fluid volumes on short- and long-term injection frequencies, visual acuity outcomes, and structural changes in the outer retina in nAMD patients.

Methods

Participants

This is a post-hoc analysis of Fight Retinal Blindness! (FRB!) Registry data from a single centre (Zürich, Switzerland). FRB! is a web-based platform that collects real-world data from clinical practice regarding outcomes of retinal diseases with well-structured assessment of medical record data.[18] Treatment-naive eyes with nAMD that were treated with a treat-and-extend regimen were included in this study. Medical records were reviewed for demographic data, best-corrected visual acuity (BCVA), number of anti-VEGF treatments, and the development of macular atrophy or fibrosis over 12 and 48 months. Patients with preexisting subfoveal atrophy or subfoveal fibrosis defined by the FRB! Registry data or other maculopathies at baseline were excluded. Spectral-domain OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) images of the macula were acquired during clinical practice routine, and volumetric macula-centred OCT scans were processed at baseline, after the first 2 initial anti-VEGF treatments (processed on the day of the third injection, which corresponded to 8 weeks after the first anti-VEGF injection) and over 12 and 48 months, respectively. Medical records in the FRB! Registry are well structured, but OCT image acquisition is not standardized. The OCT volumes available had at least 19 B-scans per volume. BCVA was measured using Snellen charts and converted to numbers of letters on the logMAR visual acuity chart. To evaluate the effect of post−initial treatment fluid volumes on BCVA, injection frequencies, and structural changes of the outer retina, fluid-volume subgroups were defined for each fluid type (i.e., IRF, SRF, and PED). The high-fluid-volume subgroup was defined as patients with the highest 25% quartile of mean residual fluid volumes in the central 6 mm after 2 initial treatments. The remaining 75% of patients were classified as the low-fluid-volume subgroup.

Automated retinal fluid quantification

Macular fluid was automatically segmented and quantified using a Medical Device Regulation (MDR)−approved AI algorithm (Fluid Monitor, RetInSight, Vienna, Austria).[13] The algorithm uses a convolutional neural network to identify fluid in each compartment. IRF, SRF, and PED are automatically segmented on the three-dimensional volumetric spectral-domain OCT (SD-OCT) image at a pixel level.[11] PED was defined as a region between the retinal pigment epithelium and Bruch's membrane with a width of at least 300 μm. The algorithm was trained using pixel-wise fluid annotation performed by expert readers with supervision from retinal specialists and validated using 10-fold cross-validation. Furthermore, this model was extensively validated and tested on large data sets including trials and real-world cohorts.[11,12,19−22] Absolute volume quantities were computed in nanoliters (1 nL = 0.001 mm^3) within the central 1, 3, and 6 mm macular fields.

Statistical analysis

Data were split between high and low macular fluid volumes after initial treatment, as described earlier, and executed for each fluid compartment. The numbers of injections between baseline and month 12 and between baseline and month 48 were compared between groups using an unpaired Student's *t* test. BCVA outcomes were compared as differences between post−initial treatment values and months 12 and 48, respectively. The visual acuity differences were compared between both groups using unpaired Student's *t* tests. In addition, multivariate mixed-effect models were calculated for the BCVA change after the initial treatment and injection frequency including all fluid volume subgroups. Combinations of fluid status were graphically illustrated for short- and long-term injection frequencies and visual acuity outcomes. New onset of atrophy or fibrosis was investigated using Cox regression models based on the fluid volume subgroup (high vs low IRF/SRF/PED fluid volume) as an independent variable. Cox regression models were executed in a univariate and multivariate manner, selecting first 1 and subsequently all individual fluid compartments. For all statistical tests, a *p* value below the significance level 0.05 was considered significant.

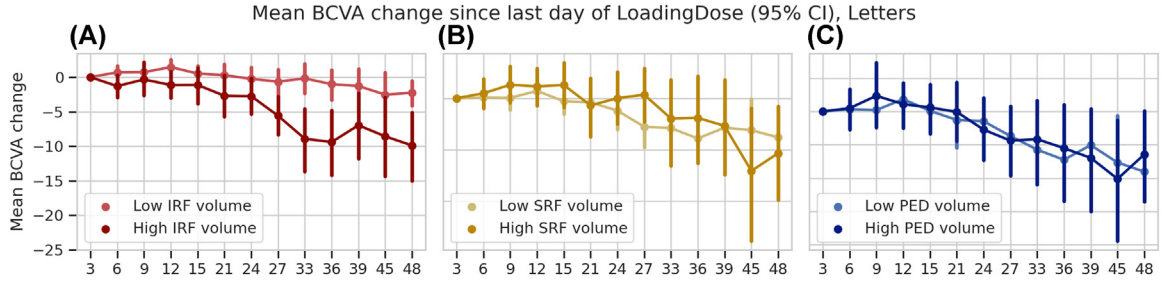

Fig. 1—Mean (95% CI) best-corrected visual acuity change after initial treatment. High (25%) vs. low (75%) fluid volumes were compared between intraretinal fluid (A, red), subretinal fluid (B, yellow), and pigment epithelium detachment (C, blue) over 48 months. Fluid volume subgroups were defined after initial treatment.

Results

A total of 209 treatment-naive eyes from 164 patients were evaluated for 48 months. Mean patient age at baseline was 78.3 years (range, 55–95 years). Fluid was analyzed in each compartment for the 2 subgroups: high (top 25%) and low (bottom 75%) amounts of residual fluid after initial treatment. The number of eyes in the high-fluid-volume subgroups were 49 and 53 for months 12 and 48, respectively. For the low-fluid-volume subgroups, the numbers of eyes for months 12 and 48 were 146 and 156, respectively. The trajectories of modeling mean BCVA after initial treatment until month 48 in each compartment are shown in Figure 1. Patients with high compared with low IRF volumes after initial treatment differed by −2.6 letters at month 12 ($p = 0.021$) and −7.4 letters at month 48 ($p = 0.007$). In addition, eyes with high IRF volumes after initial treatment received significantly more treatments, with mean differences at 12 and 48 months of +1.6 ($p < 0.001$) and +5.3 ($p = 0.002$) injections, respectively, as shown in Figure 2. Patients with high SRF volumes after initial treatment had no statistically significant difference in BCVA outcomes compared with the low-SRF subgroup. However, there were significantly more injections in the high-SRF subgroup, with mean differences at 12 and 48 months of +2.4 injections ($p < 0.001$) and +11.4 injections ($p < 0.001$), respectively. Analysis of the PED compartment showed similar results as SRF, with no statistically significant difference in BCVA outcomes between high- and low-volume subgroups but increased treatment need in the high-PED-volume group after initial treatment. The mean differences between the number of injections in patients with high compared with low PED after initial treatment at 12 and 48 months were +1.2 ($p = 0.001$) and +7.8 ($p < 0.001$), respectively.

Multivariate models for BCVA at month 12 revealed a significant result for IRF ($p = 0.022$) but not for SRF ($p = 0.575$) and PED ($p = 0.984$), in accordance with the primary calculations. For the injection frequency up to month 12, IRF and SRF still presented with significantly different numbers of injections ($p = 0.002$ and $p < 0.001$, respectively), whereas PED was nonsignificant ($p = 0.677$).

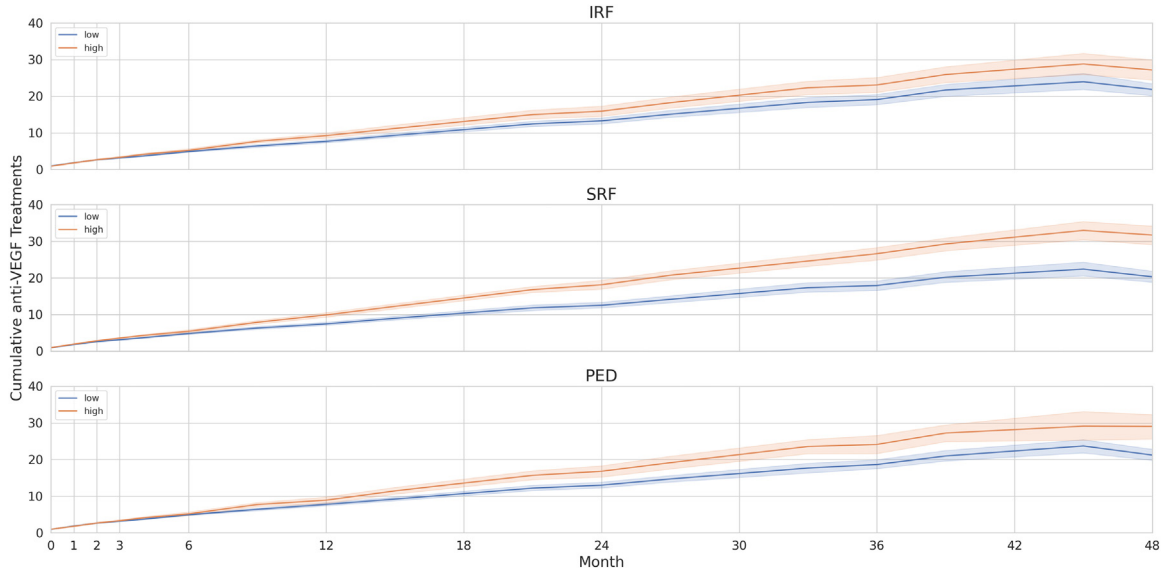

Fig. 2—Mean cumulative number of injections split between high (25%) and low (75%) fluid volumes of intraretinal fluid (A), subretinal fluid (B), and pigment epithelium detachment (C) over 48 months. Note that the slight decrease in the mean after month 45 is due to a decreased number of eyes available.

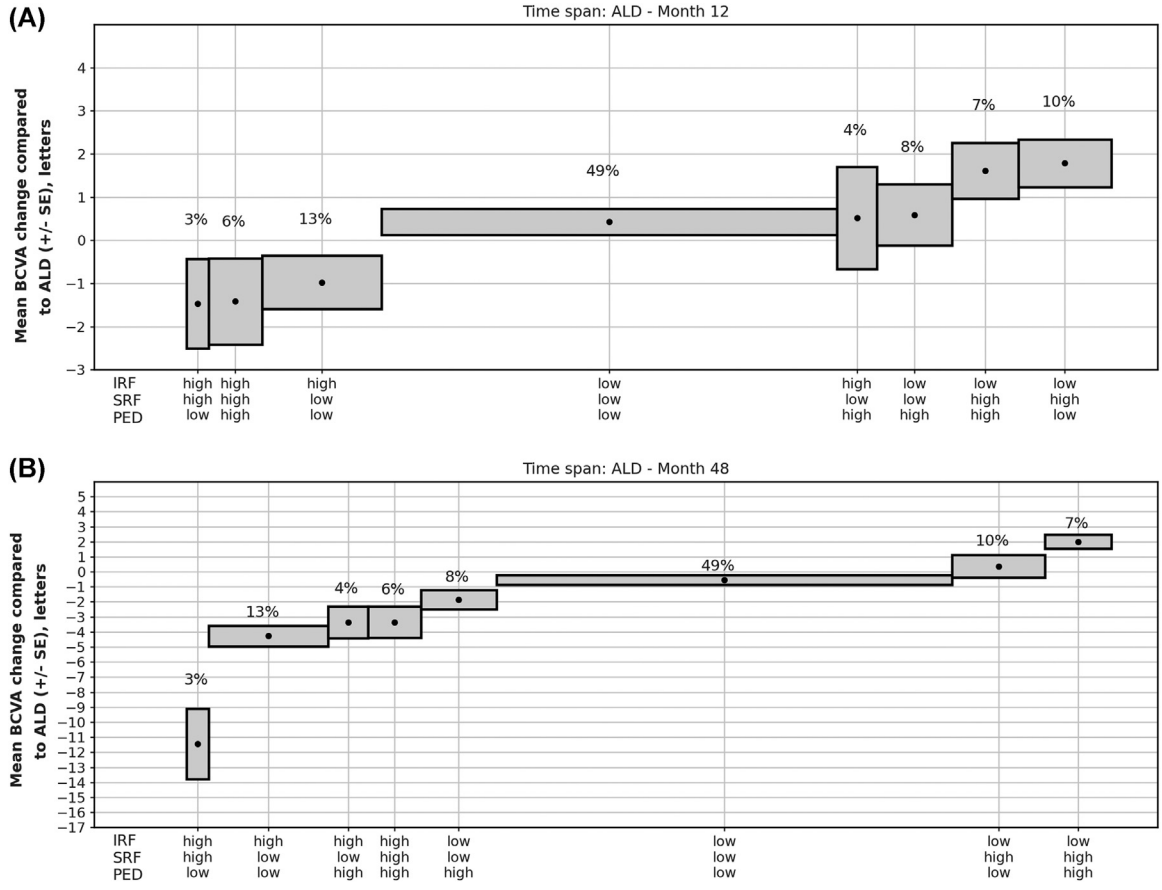

Fig. 3—Effect of combinations of high (25%) and low (75%) fluid volumes of intraretinal fluid, subretinal fluid, and pigment epithelium detachment on best-corrected visual acuity after initial treatment: (A) 12 months, (B) 48 months.

For BCVA at month 48, IRF was the only significant variable in the multivariate model ($p < 0.001$), which is again in concordance with the primary calculations. The results for the injection frequency up to month 48 did not differ from the univariate analysis, and all fluid compartments showed significant differences (IRF, $p = 0.015$; SRF, $p < 0.001$; PED, $p = 0.040$).

The comparative boxplots (Fig. 3) showed that most patients (49%) were classified with a low amount of fluid after the initial treatment in all 3 compartments. Despite a significantly lower number of treatments, particularly considering 48-month follow-up, this group did not show the best BCVA outcomes. Better visual outcomes were present in patients with high volumes of SRF in this study. In contrast, patients who presented with high IRF volumes were more likely to lose BCVA over 12 and 48 months, respectively. If patients had high IRF and SRF volumes, the negative effect of the high IRF level appeared to be dominant. Furthermore, patients with high fluid volumes after the initial treatment in all 3 compartments had increased treatment needs (Fig. 4). However, in the case of high IRF volumes, even by increasing treatment frequency, the visual outcomes were limited, indicating a greater chance of long-term sequelae.

For the analysis of new-onset atrophy and fibrosis, eyes with a minimum of 2 years of follow-up were included to ensure a clinically meaningful sample for the development of atrophy and fibrosis. Eyes with subfoveal and (or) parafoveal atrophy were excluded. Therefore, 22 eyes from 15 patients were excluded from the sample. Thus, 187 eyes from 149 patients remained in the data set for this analysis. Macular atrophy occurred in 71 of 187 eyes (40%). The higher 25% IRF fluid volume subgroup showed 1.81 times higher risk of developing atrophy ($p = 0.016$) compared with the lower 75% fluid volume subgroup in the univariate model. In the univariate model, high SRF volume showed −0.92 times the risk of developing atrophy. Although the effect was small, it was still statistically significant ($p = 0.007$). In the multivariate model, a high IRF level was still associated with higher risk ($p = 0.011$) and a high SRF level with lower risk ($p = 0.006$) of the development of macular atrophy. In either model, PED volumes after initial treatment were not associated with atrophy development. Fibrosis development was present in 43 of the 187 eyes (23%). However, there were no significant differences between the high- and low-volume subgroups after the initial treatment in all fluid compartment (i.e., SRF, IRF, and

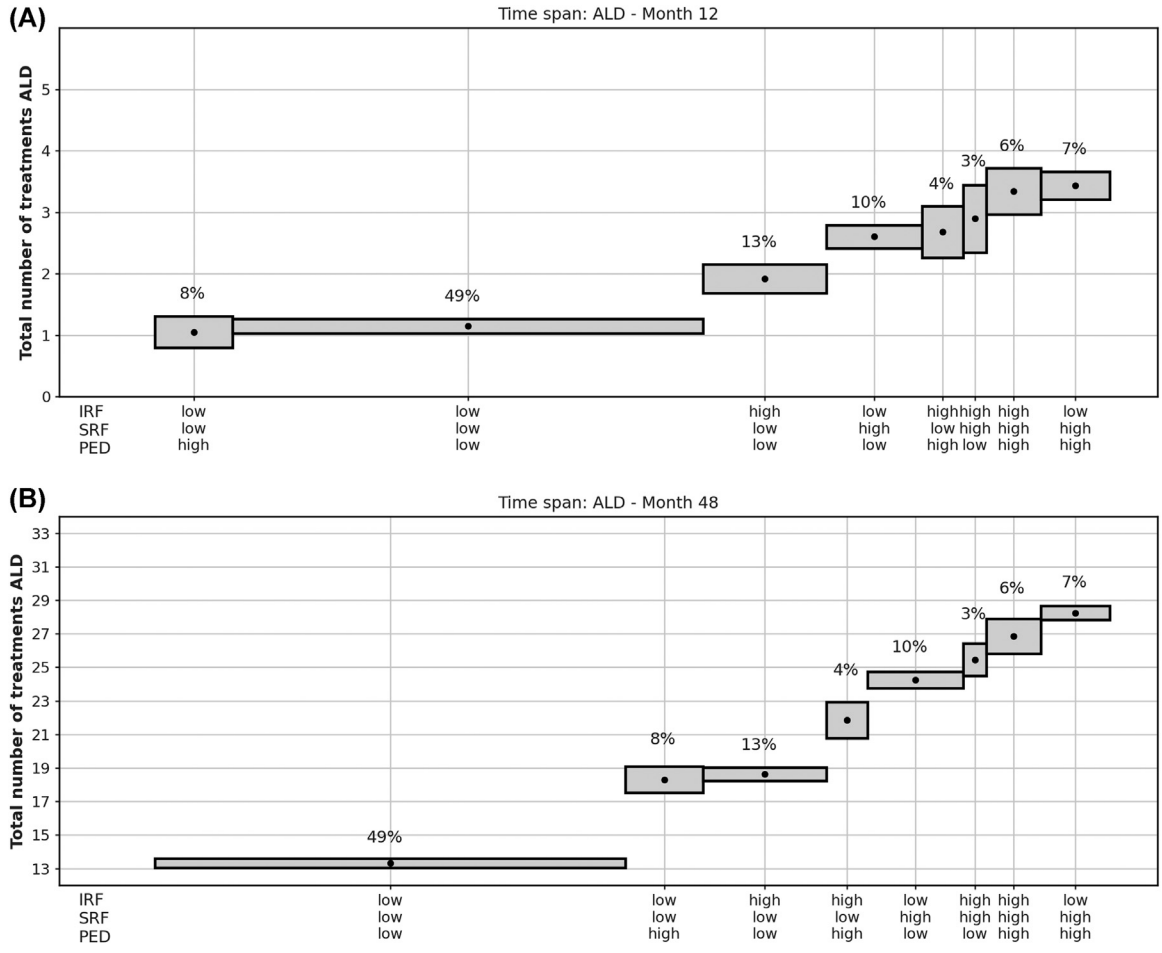

Fig. 4—Effect of combinations of high (25%) and low (75%) fluid volumes of intraretinal fluid, subretinal fluid, and pigment epithelium detachment on best-corrected visual acuity after initial treatment: (A) 12 months, (B) 48 months.

PED) in the univariate and multivariate models (all $p > 0.05$).

Discussion

Anti-VEGF therapy in nAMD became a major milestone for the continuous management of patients.[23] The treatment is highly effective, but real-world outcomes are often suboptimal when compared with clinical trials. Reasons for this may be the strict treatment adherence and treatment per protocol in clinical trials, as well as strict inclusion and exclusion criteria, especially considering the presence of macular atrophy and fibrosis. Furthermore, these features may be less frequent at initial presentation but develop over time. While clinical studies often report 12- or 24-month outcomes, real-world studies can be used to investigate long-term progression of the underlying disease.[24] In our study we found that eyes that present with high IRF volumes are prone to worse visual outcomes than eyes with low IRF volumes, which is in agreement to previous studies.[12] In addition, these eyes receive significantly more injections during their follow-ups, increasing the burden on patients and health institutions. In contrast to IRF volumes, high SRF and PED volumes did not result in worse BCVA outcomes but required more injections to maintain the same visual acuity as those with low SRF and PED volumes. Higher volumes of fluid are the driving force for anti-VEGF retreatments in all fluid compartments. Fluid is still the most important biomarker of disease activity, tailoring treatment decisions and prognosis in nAMD. Fluid compartments and their volumes matter in terms of treatment need and visual outcomes.[15,25] Thus, a deep understanding of the individual retinal fluid dynamics through a real-time quantification model may enable a more personalize anti-VEGF treatment regimen. Additionally, the possibility of better management of resources reduces the burden on patients without compromising outcomes in clinical practice.[26]

Based on our findings, strategies to dry the retina and maintain a dry state for a longer period are important to counteract vision loss in nAMD. Although this is a post hoc analysis, our results are a good asset to the FLUID study.[27] Whereas we found an increased number of injections for the high-SRF subgroup with no difference in visual acuity outcomes, the FLUID study reported fewer injections for the tolerant SRF group with noninferior visual acuity

gains.[28] The difference between our study and the FLUID study is that the FLUID study intentionally tolerated SRF, whereas a high SRF volume in our study was counteracted with a higher number of injections. Overall, inactive persistent SRF may not be harmful in some patients if appropriately considered. However, in another post hoc analysis of the FLUID study, our group was able to show that SRF fluid volumes did not differ significantly between the treatment arms in the FLUID study.[20] Further, if left untreated in eyes with active disease, SRF volumes may increase and negatively affect short-term visual acuity.[21] To summarize the findings on SRF, patients with active disease and high volumes after initial treatment, indicating disease activity, are more likely to require more treatments in the real world. If these patients can be identified, BCVA outcomes may be maintained.

Development of macular atrophy and fibrosis is important for long-term visual acuity results. We found 40% of eyes developing atrophy at the end of the 48 months of follow-up, showing a high incidence in our sample. Although the origins of macular atrophy remain unclear, it is known that photoreceptor integrity loss is an early stage of atrophy progression. In our analysis, IRF was the only fluid biomarker significantly related to the onset of atrophy, with a 1.81 higher risk of its development in the high-IRF-volume subgroup. Interestingly, high volumes of SRF after initial treatment were associated with a lower risk of developing macular atrophy. This is in accordance with a qualitative evaluation of fluid types in a real-world data set.[29] Further, 23% of eyes developed fibrosis at the end of the 48 months of follow-up. There was no association with fluid in any compartment after the initial treatment with fibrosis development in our data. Previous study showed a correlation between IRF at baseline or predominantly persistent IRF and fibrosis development.[18,29] In contrast to our study, fluid compartments were only assessed qualitatively, not quantitatively.

Previous publications correlated late-stage morphologic outcomes such as fibrosis and atrophy with MNV types.[30,31] The development of a subretinal type I MNV may be protective against macular atrophy.[32] In our Cox regression model we found a slight protective effect of SRF on developing atrophy. Patients with type III MNV, in contrast, can develop extensive atrophy with associated visual acuity loss.[33] Ultimately, MNV gradings were not available in the FRB! Registry data. A possible association of predominantly IRF, type III MNV, and the development of macular atrophy appears plausible. The same holds true for type I MNV, SRF, and decelerated retinal pigment epithelium degeneration. However, the absence of MNV gradings in the FRB! Registry must be mentioned as a limitation of our study together with an absence of fluorescein angiography imaging for determining MNV types. In addition, other imaging modalities such as OCT angiography could incorporate important information such as MNV membrane size or various vessel characteristics and their anatomic responses to anti-VEGF treatment for subsequent analyses. The addition of lesion type and MNV characteristics might be an important predictor for patient outcomes. In real-world management of nAMD, differentiation of lesion types is not frequently performed because treatment is based mainly on OCT and fluid characteristics. Therefore, we believe that the differentiation of lesion type does not add to the information gained by this analysis. Another limitation of this study is its post hoc character and the nonuniform OCT acquisition. OCT volumes with higher B-scan density are preferred for more precise fluid quantifications. Furthermore, this is a single-centre FRB! Registry data set analysis, and therefore, the results can only be generalized to this specific population. AI is an evolving technology, and thus segmentation errors and lack of generalizability are still limitations inherent to studies using AI-based algorithms. However, the fluid monitor is an MDR-approved device that has been used in previous data sets, including real-world cohorts, and has been tested in clinical practice.[34,35] The tool provides valuable insights and assists physicians in making more informed decisions, but the final judgment and treatment decision belong to the physician.

In summary, we were able to present an analysis of FRB! Registry data showing that increased volumes of fluid after initial treatment are associated with increased numbers of injections in nAMD. This finding is valid for IRF, SRF, and PED. For SRF and PED, higher numbers of injections can counteract visual acuity loss in short- and long-term results. High volumes of IRF still required more injections, but the increased number of injections did not compensate for the loss of visual acuity in the high-IRF subgroup. Further, the high-IRF subgroup was more likely to develop macular atrophy, indicating its contribution to irreversible lost of visual function. Identification of patients with high and low fluid volumes and the use of their information to personalize treatment regiments may be keys to improving management of nAMD in the real world. With the help of automated fluid quantifications using AI, we can tailor individual treatment regimens, predict the risk of disease progression, and use this information to increase patient adherence during their lifelong disease management.

References

1. Bourne RRA, Jonas JB, Bron AM, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. Br J Ophthalmol 2018;102:575–85.
2. Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204–22.
3. Guymer RH, Campbell TG. Age-related macular degeneration. Lancet 2023;401:1459–72.
4. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular

degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014;98:1144–67.
5. Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus nomenclature for reporting neovascular age-related macular degeneration data. Ophthalmology 2020;127:616–36.
6. Maguire MG, Martin DF, Ying G, et al. Five-year outcomes with anti–vascular endothelial growth factor treatment of neovascular age-related macular degeneration. Ophthalmology 2016;123:1751–61.
7. Ciulla TA, Hussain RM, Pollack JS, Williams DF. Visual acuity outcomes and anti–vascular endothelial growth factor therapy intensity in neovascular age-related macular degeneration patients. Ophthalmol Retina 2020;4:19–30.
8. Khanani AM, Skelly A, Bezlyak V, Griner R, Torres LR, Sagkriotis A. SIERRA-AMD: a retrospective, real-world evidence study of patients with neovascular age-related macular degeneration in the United States. Ophthalmol Retina 2020;4:122–33.
9. Chakravarthy U, Havilio M, Syntosi A, et al. Impact of macular fluid volume fluctuations on visual acuity during anti-VEGF therapy in eyes with nAMD. Eye (Lond) 2021;35:2983–90.
10. Reiter GS, Schmidt-Erfurth U. Quantitative assessment of retinal fluid in neovascular age-related macular degeneration under anti-VEGF therapy. Ther Adv Ophthalmol 2022;14:251584142210833.
11. Schlegl T, Waldstein SM, Bogunovic H, et al. Fully automated detection and quantification of macular fluid in OCT using deep learning. Ophthalmology 2018;125:549–58.
12. Schmidt-Erfurth U, Mulyukov Z, Gerendas BS, et al. Therapeutic response in the HAWK and HARRIER trials using deep learning in retinal fluid volume and compartment analysis. Eye (Lond) 2023;37:1160–9.
13. Schmidt-Erfurth UM, Vogl W, Jampol LM, Bogunović H. Application of automated quantification of fluid volumes to anti-VEGF therapy of neovascular age-related macular degeneration. Ophthalmology 2020;127:1211–9.
14. De Fauw J, Ledsam JR, Romera-Paredes B, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nat Med 2018;24:1342–50.
15. Bogunović H, Mares V, Reiter GS, Schmidt-Erfurth U. Predicting treat-and-extend outcomes and treatment intervals in neovascular age-related macular degeneration from retinal optical coherence tomography using artificial intelligence. Front Med 2022;9:2175.
16. Sharma S, Toth CA, Daniel E, et al. Macular morphology and visual acuity in the second year of the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology 2016;123:865–75.
17. Schmidt-Erfurth U, Waldstein SM. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. Prog Retin Eye Res 2016;50:1–24.
18. Nguyen V, Barthelmes D, Gillies MC. Neovascular age-related macular degeneration: a review of findings from the real-world Fight Retinal Blindness! Registry. Clin Exp Ophthalmol 2021;49:652–63.
19. Gerendas BS, Sadeghipour A, Michl M, et al. Validation of an automated fluid algorithm on real-world data of neovascular age-related macular degeneration over five years. Retina 2022;42:1673–82.
20. Reiter GS, Grechenig C, Vogl W-D, et al. Analysis of fluid volume and its impact on visual acuity in the FLUID study as quantified with deep learning. Retina 2021;41:1318–28.
21. Grechenig C, Reiter GS, Riedl S, et al. Impact of residual subretinal fluid volumes on treatment outcomes in a subretinal fluid–tolerant treat-and-extend regimen. Retina 2021;41:2221–8.
22. Mares V, Schmidt-Erfurth UM, Leingang O, et al. Approved AI-based fluid monitoring to identify morphological and functional treatment outcomes in neovascular age-related macular degeneration in real-world routine (FRB!). Br J Ophthalmol 2023 bjo-2022-323014.
23. Rosenfeld PJ. Optical coherence tomography and the development of antiangiogenic therapies in neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 2016;57:OCT14.
24. Martin-Pinardel R, Izquierdo-Serra J, De Zanet S, et al. Artificial intelligence–based fluid quantification and associated visual outcomes in a real-world, multicentre neovascular age-related macular degeneration national database. Br J Ophthalmol 2023;0 bjo-2022-322297.
25. Maunz A, Barras L, Kawczynski MG, et al. Machine learning to predict response to ranibizumab in neovascular age-related macular degeneration. Ophthalmol Sci 2023;3:100319.
26. Pucchio A, Krance SH, Pur DR, et al. Applications of artificial intelligence and bioinformatics methodologies in the analysis of ocular biofluid markers: a scoping review. Graefes Arch Clin Exp Ophthalmol 2023;10. doi: 10.1007/s00417-023-06100-6.
27. Arnold JJ, Markey CM, Kurstjens NP, Guymer RH. The role of sub-retinal fluid in determining treatment outcomes in patients with neovascular age-related macular degeneration—a phase IV randomised clinical trial with ranibizumab: The FLUID study. BMC Ophthalmol 2016;16:1–9.
28. Guymer RH, Markey CM, McAllister IL, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen. Ophthalmology 2019;126:723–34.
29. Llorente-González S, Hernandez M, González-Zamora J, et al. The role of retinal fluid location in atrophy and fibrosis evolution of patients with neovascular age-related macular degeneration long-term treated in real world. Acta Ophthalmol 2022;100 aos.14905.
30. Borrelli E, Mastropasqua L, Souied E, et al. Longitudinal assessment of type 3 macular neovascularization using 3D volume-rendering OCTA. Can J Ophthalmol 2022;57:228–35.
31. Mathis T, Holz FG, Sivaprasad S, et al. Characterisation of macular neovascularisation subtypes in age-related macular degeneration to optimise treatment outcomes. Eye (Lond) 2022;2022:1–8.
32. Fukuyama H, Huang BB, BouGhanem G, Fawzi AA. The fovea-protective impact of double-layer sign in eyes with foveal-sparing geographic atrophy and age-related macular degeneration. Invest Ophthalmol Vis Sci 2022;63:4.
33. Ernest J, Manethova K, Kolar P, Sobisek L, Sacconi R, Querques G. One-year results of fixed aflibercept treatment regime in type 3 neovascularization. Ophthalmologica 2020;243:58–65.

34. Schmidt-Erfurth U, Reiter GS, Riedl S, et al. AI-based monitoring of retinal fluid in disease activity and under therapy. Prog Retin Eye Res 2022;86:100972.
35. Coulibaly LM, Sacu S, Fuchs P, et al. Personalized treatment supported by automated quantitative fluid analysis in active neovascular age-related macular degeneration (nAMD)—a phase III, prospective, multicentre, randomized study: design and methods. Eye (Lond) 2023;37:1464–9.

Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

Gregor S. Reiter received research funds from RetInSight. Hrvoje Bogunovic received research funds from Heidelberg Engineering and Apellis. Ursula Schmidt-Erfurth is a scientific consultant for Genentech, Heidelberg Engineering, Kodiak, RetInSight, Novartis, and Roche.

From the *Laboratory for Ophthalmic Image Analysis, Department of Ophthalmology and Optometry, Medical University of Vienna, Vienna, Austria; †Department of Ophthalmology, Federal University of Minas Gerais, Belo Horizonte, Brazil; ‡Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland.

Parts of this work was presented at the 45th Annual Meeting of the Macula Society, Berlin, Germany, June 8—11, 2022.

Originally received Jul. 13, 2023. Final revision Oct. 9, 2023. Accepted Oct. 28, 2023.

Correspondence to: Ursula Schmidt-Erfurth, MD, Department of Ophthalmology and Optometry, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. ursula.schmidt-erfurth@meduniwien.ac.at.