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Association between subretinal fluid and long-term visual outcomes to anti-VEGF therapy in wet age-related macular degeneration

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Short title: Subretinal fluid and anti-VEGF therapy

Key messages: Subretinal fluid presence was not associated with worse visual acuity at 2-year follow-up after anti-VEGF treatment. Our findings indicate that residual SRF may be tolerated without compromising visual prognosis, whereas IRF remains associated with poorer visual acuity.

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Abstract

Purpose: To evaluate the association between subretinal fluid and functional outcomes in patients with wet age-related macular degeneration (AMD) treated with anti-VEGF therapy.

Methods: Clinical cohort study of a total of 441 eyes from 441 patients with wet AMD with a follow-up of 2 years.

Results: Cohort mean age was 80.0 ± 8.1 years with sex distribution 35% male and 65% female. Following anti-VEGF therapy, mean best-corrected visual acuity (BCVA) improved from 0.52 ± 0.34 logMAR units at baseline to 0.46 ± 0.32 logMAR units after induction, 0.40 ± 0.27 logMAR units at 1-year and 0.40 ± 0.29 logMAR units at 2-years, while central retinal thickness decreased from 397 ± 159 μm to 307 ± 125 μm after induction, 273 ± 101 μm at 1-year and 259 ± 84 μm at 2-years. Intraretinal fluid was present in 55% of eyes at baseline, 26% after induction, 25% at 1-year and 24% at 2-years and was associated with worse BCVA at all timepoints ($P < 0.05$ for all). On the contrary, subretinal fluid was present in 59% of eyes at baseline, 31% after induction, 26% at 1-year and 22% at 2-years, and in none of the follow-up timepoints after anti-VEGF treatment it associated with BCVA worsening ($P > 0.05$ for all).

Conclusions: Intraretinal fluid was consistently associated with poorer visual acuity, whereas subretinal fluid presence in the eye did not associate with worse visual outcomes in anti-VEGF-treated wet AMD. These findings suggest that residual subretinal fluid may be tolerated without compromising visual prognosis.

Keywords: anti-VEGF, central retinal thickness, intraretinal fluid, subretinal fluid, visual acuity, wet age-related macular degeneration

Introduction

Age-related macular degeneration (AMD) is one of the leading causes of irreversible vision loss among the elderly in developed countries [1,2]. Although dry AMD accounts for the majority of the cases, wet AMD is responsible for most cases of severe central vision loss due to its rapid progression and aggressive disease course [3,4]. Wet AMD is characterized by pathological choroidal neovascularization in which abnormal blood vessels originating from the choroid grow through defects in Bruch's membrane into the subretinal space [5,6]. The pathophysiology involves a complex interaction between age-related changes in the retinal pigment epithelium, oxidative stress, chronic inflammation, impaired choroidal circulation, and upregulation of angiogenic factors, particularly vascular endothelial growth factor (VEGF) [6,7].

Intravitreal anti-VEGF therapy has become the standard of care for wet AMD and has demonstrated significant efficacy in reducing macular fluid, preventing further neovascular growth, and stabilizing or improving visual acuity in many patients [8-10]. Although anti-VEGF therapy is effective for most patients with wet AMD, some eyes show persistent disease activity despite repeated injections [11]. Numerous studies have demonstrated that the presence of intraretinal fluid (IRF) is associated with worse visual outcomes, whereas the prognostic significance of subretinal fluid (SRF) is less consistent [12-14]. It is even considered that small amounts of persistent SRF may act as a protective factor [12]. This raises the question of whether strict elimination of all SRF is necessary before extending treatment intervals, or whether small amounts of persistent SRF could be tolerated without compromising visual outcomes, thereby potentially reducing the number of injections and overall treatment burden.

The disease often requires long-term monitoring and treatment, pushing emphasis on cost-effective treatment strategies and identification of reliable indicators of treatment success [15]. Here, we aimed to assess the role of subretinal fluid as a treatment target in wet AMD.

Methods

Study design

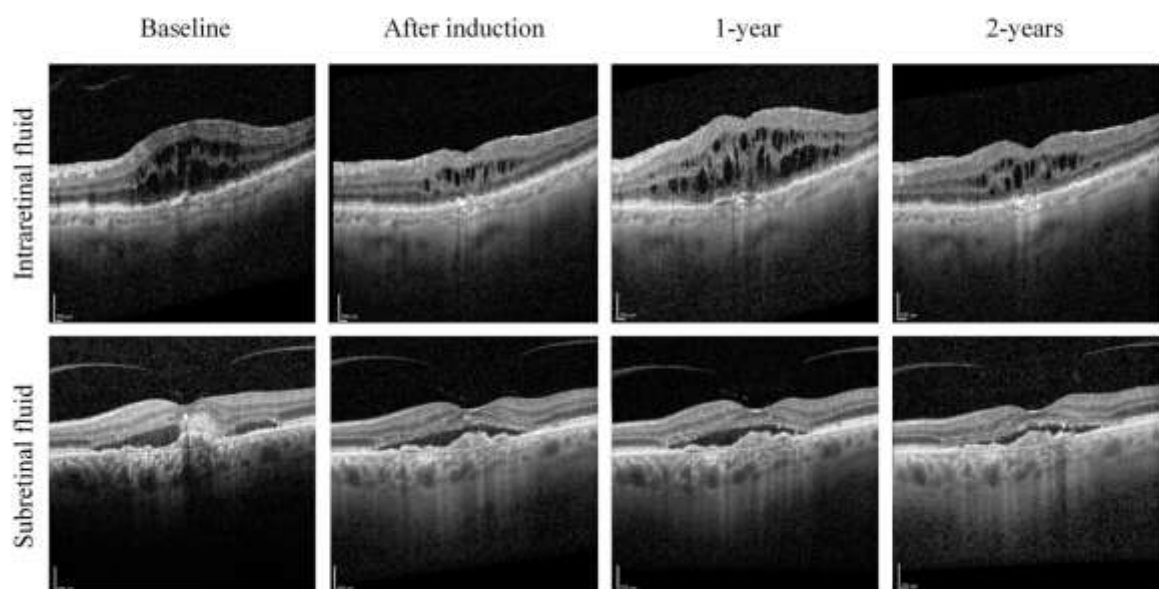
This study includes a clinical cohort of wet AMD patients treated at the Department of Ophthalmology, Mehiläinen Hospital, Helsinki, Finland, with anti-VEGFs according to the National Current Care Guideline for the disease. All eyes were managed with a treat-and-extend regimen (TER) protocol, and only patients with unilateral disease were included.

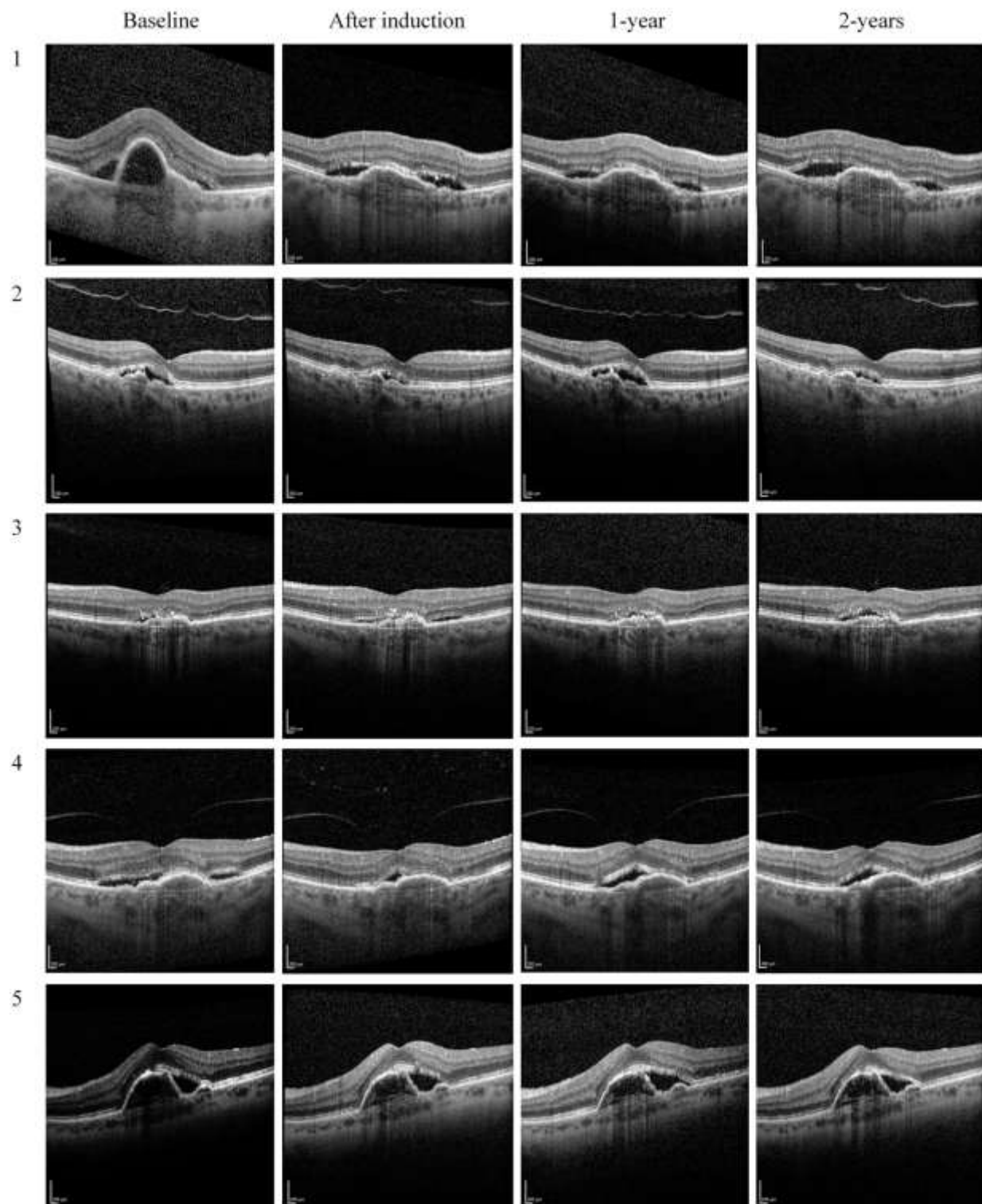
The effect of fluid at different timepoints was analyzed against visual acuity outcomes. The study was approved by the Medical Research Ethics Committee (THL/587/14.02.00/2025 FD:0074000125), and it adhered to the tenets of the Declaration of Helsinki.

Clinical evaluation

Best-corrected visual acuity (BCVA) was recorded in ETDRS letters. Retinal anatomy was evaluated using spectral-domain optical coherence tomography (SD-OCT; Heidelberg Engineering, Heidelberg, Germany), including central retinal thickness (CRT) and the presence of IRF and SRF (Figure 1 and Online Resource 1).

Figure 1



Subretinal fluid

Outcomes were assessed after the induction phase with the first anti-VEGF drug, at 1 year, and at 2 years.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation, and categorical variables as proportions. For two-group comparisons, non-parametric variables were analyzed with the Mann-Whitney U-test and continuous variables with the Student's T-test. All tests were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 31.0.2.0 (IBM Corp., Armonk, N.Y.).

Results

A total of 441 eyes from 441 patients with wet AMD were included, with a mean age of 80.0 ± 8.1 years. Female patients constituted 65% of the cohort. The majority of eyes received bevacizumab (69%), followed by aflibercept (23%) and faricimab (8%).

Baseline BCVA was 0.52 ± 0.34 logMAR units, and CRT 397 ± 159 μm . After the induction phase, BCVA improved to 0.46 ± 0.32 logMAR units and stabilized at 0.40 ± 0.27 logMAR units at 1-year and 0.40 ± 0.29 logMAR units at 2-years, while CRT decreased to 307 ± 125 μm , 273 ± 101 μm and 259 ± 84 μm at the corresponding timepoints.

The prevalence of intraretinal fluid (IRF) decreased from 55% at baseline to 26% after induction, 25% at 1-year, and 24% at 2-years. Subretinal fluid (SRF) was present in 59% of eyes at baseline, 31% after induction, 26% at 1-year, and 22% at 2-years (Table 1).

Table 1. Clinical characteristics of wAMD patients

Parameter	
Age (years)	80.0 ± 8.1
Male : Female	155 : 286 (35 : 65)
Anti-VEGF (n/%)	
Bevacizumab	303 (69)
Aflibercept	103 (23)
Faricimab	35 (8)
BCVA (logMAR)	
Baseline	0.52 ± 0.34
After induction phase	0.46 ± 0.32
1-year	0.40 ± 0.27
2-years	0.40 ± 0.29
CRT (μm)	
Baseline	397 ± 159
After induction phase	307 ± 125
1-year	273 ± 101
2-years	259 ± 84
Intraretinal fluid (%)	
Baseline	55
After induction phase	26
1-year	25
2-years	24
Subretinal fluid (%)	
Baseline	59
After induction phase	31
1-year	26
2-years	22

Data are given as mean $\pm$ SD or proportions. BCVA; best-corrected visual acuity, CRT; central retinal thickness.

Effect of intraretinal fluid on visual outcomes

Eyes with IRF at baseline had significantly worse BCVA compared with eyes without IRF (0.59 ± 0.37 vs 0.43 ± 0.27 logMAR units, $P < 0.001$), and this difference remained after the induction phase (0.52 ± 0.34 vs 0.40 ± 0.29 logMAR units, $P < 0.001$) as well as at 1- and 2-year follow-up ($P = 0.003$ and $P = 0.014$) (Table 2).

Table 2. Anatomical and functional outcomes in regard to intraretinal fluid status.

Parameter	Intraretinal fluid at baseline		P-value
	No	Yes	
BCVA (logMAR)			
Baseline	0.43 ± 0.27	0.59 ± 0.37	<0.001
After induction phase	0.40 ± 0.29	0.52 ± 0.34	<0.001
1-year	0.36 ± 0.27	0.43 ± 0.27	0.003
2-years	0.36 ± 0.29	0.43 ± 0.28	0.014
Intraretinal fluid after induction phase			
	No	Yes	P-value
BCVA (logMAR)			
After induction phase	0.43 ± 0.32	0.55 ± 0.32	<0.001
1-year	0.37 ± 0.27	0.46 ± 0.26	0.002
2-years	0.37 ± 0.28	0.47 ± 0.28	0.004
Intraretinal fluid at 1-year			
	No	Yes	P-value
BCVA (logMAR)			
1-year	0.38 ± 0.26	0.46 ± 0.30	0.028
2-years	0.38 ± 0.30	0.45 ± 0.24	0.014
Intraretinal fluid at 2-years			
	No	Yes	P-value
BCVA (logMAR)			
2-years	0.38 ± 0.29	0.46 ± 0.29	0.017
Intraretinal fluid at any timepoint			
Parameter	No	Yes	P-value
BCVA (logMAR)			
Baseline	0.41 ± 0.27	0.57 ± 0.35	<0.001
After induction phase	0.36 ± 0.27	0.51 ± 0.33	<0.001
1-year	0.32 ± 0.24	0.44 ± 0.28	<0.001
2-years	0.29 ± 0.22	0.45 ± 0.31	<0.001

Data are given as mean $\pm$ SD. For two-group comparisons, non-parametric variables were analyzed with the Mann-Whitney U-test and continuous variables with the Student's T-test. Bold = $P < 0.05$.

Similarly, eyes with IRF after induction had worse BCVA compared with those without IRF at the end of the induction phase (0.55 ± 0.32 vs 0.43 ± 0.32 logMAR units, $P < 0.001$), at 1-year (0.46 ± 0.26 vs 0.37 ± 0.27 logMAR units, $P = 0.002$) and 2-years (0.47 ± 0.28 vs 0.37 ± 0.28 logMAR units, $P = 0.004$) (Table 2). At the 1-year and 2-year timepoints, eyes with IRF continued to demonstrate inferior BCVA values compared with those without IRF ($P < 0.05$, Table 2).

When comparing eyes having IRF at any timepoint during follow-up against those without IRF across any timepoint, eyes with IRF consistently exhibited worse BCVA, including baseline (0.57 ± 0.35 vs 0.41 ± 0.27 logMAR units, $P < 0.001$), after the induction phase (0.51 ± 0.33 vs 0.36 ± 0.27 logMAR units, $P < 0.001$), at 1-year (0.44 ± 0.28 vs 0.32 ± 0.24 logMAR units, $P < 0.001$) and at 2-years (0.45 ± 0.31 vs 0.29 ± 0.22 logMAR units, $P < 0.001$) (Table 2).

Effect of subretinal fluid on visual outcomes

Eyes with SRF at baseline had worse BCVA compared with eyes without SRF (0.56 ± 0.34 vs 0.45 ± 0.33 logMAR units, $P < 0.001$, Table 3).

Table 3. Anatomical and functional outcomes in regard subretinal fluid status.

Parameter	Subretinal fluid at baseline		P-value
	No	Yes	
BCVA (logMAR)			
Baseline	0.45 ± 0.33	0.56 ± 0.34	<0.001
After induction phase	0.44 ± 0.33	0.48 ± 0.32	<u>0.489</u>
1-year	0.40 ± 0.29	0.40 ± 0.26	<u>0.164</u>
2-years	0.43 ± 0.33	0.38 ± 0.26	<u>0.303</u>
CRT (μm)			
Baseline	337 ± 134	441 ± 161	<0.001
After induction phase	287 ± 105	322 ± 136	0.003
1-year	262 ± 94	280 ± 105	0.089
2-years	243 ± 69	270 ± 91	0.010

Data are given as mean $\pm$ SD. For two-group comparisons, non-parametric variables were analyzed with the Mann-Whitney U-test and continuous variables with the Student's T-test. Bold = $P < 0.05$.

However, no statistically significant differences in BCVA were observed after the induction phase, at 1-year, or at 2-years (Table 3). No statistically significant differences in BCVA were observed when having SRF after the induction phase, at the 1-year or at the 2-year timepoint compared to those without SRF at the given timepoint (Online Resources 2-4).

Online Resource 2. Anatomical and functional outcomes in regard subretinal fluid status.

Parameter	Subretinal fluid after induction phase		
	No	Yes	P-value
BCVA (logMAR)			
After induction phase	0.45 ± 0.33	0.48 ± 0.30	0.226
1-year	0.40 ± 0.28	0.39 ± 0.24	0.451
2-years	0.41 ± 0.31	0.36 ± 0.23	0.465
CRT (μm)			
After induction phase	272 ± 101	386 ± 139	<0.001
1-year	251 ± 84	315 ± 112	<0.001
2-years	244 ± 83	284 ± 78	<0.001

Data are given as mean ± SD. For two-group comparisons, non-parametric variables were analyzed with the Mann-Whitney U-test and continuous variables with the Student's T-test. Bold = P<0.05.

Online Resource 3. Anatomical and functional outcomes in regard subretinal fluid status.

Parameter	Subretinal fluid at 1-year		
	No	Yes	P-value
BCVA (logMAR)			
1-year	0.41 ± 0.28	0.36 ± 0.25	0.236
2-years	0.41 ± 0.30	0.36 ± 0.26	0.369
CRT (μm)			
1-year	259 ± 86	330 ± 101	<0.001
2-years	245 ± 71	284 ± 83	<0.001

Data are given as mean ± SD. For two-group comparisons, non-parametric variables were analyzed with the Mann-Whitney U-test and continuous variables with the Student's T-test. Bold = P<0.05.

Online Resource 4. Anatomical and functional outcomes in regard subretinal fluid status.

Parameter	Subretinal fluid at 2-years		
	No	Yes	P-value
BCVA (logMAR)			
2-years	0.41 ± 0.30	0.36 ± 0.26	0.402
CRT (μm)			
2-years	249 ± 83	294 ± 79	<0.001

Data are given as mean ± SD. For two-group comparisons, non-parametric variables were analyzed with the Mann-Whitney U-test and continuous variables with the Student's T-test. Bold = P<0.05.

In eyes having SRF at any timepoint during follow-up, BCVA at baseline, after the induction phase, at 1-year or at 2-years were comparable to those without SRF at any timepoint (Table 4).

Furthermore, in eyes with SRF at all timepoints, no statistically significant differences in BCVA at baseline, after the induction phase, at 1-year or at 2-years were observed compared with eyes without persistent SRF (Table 4).

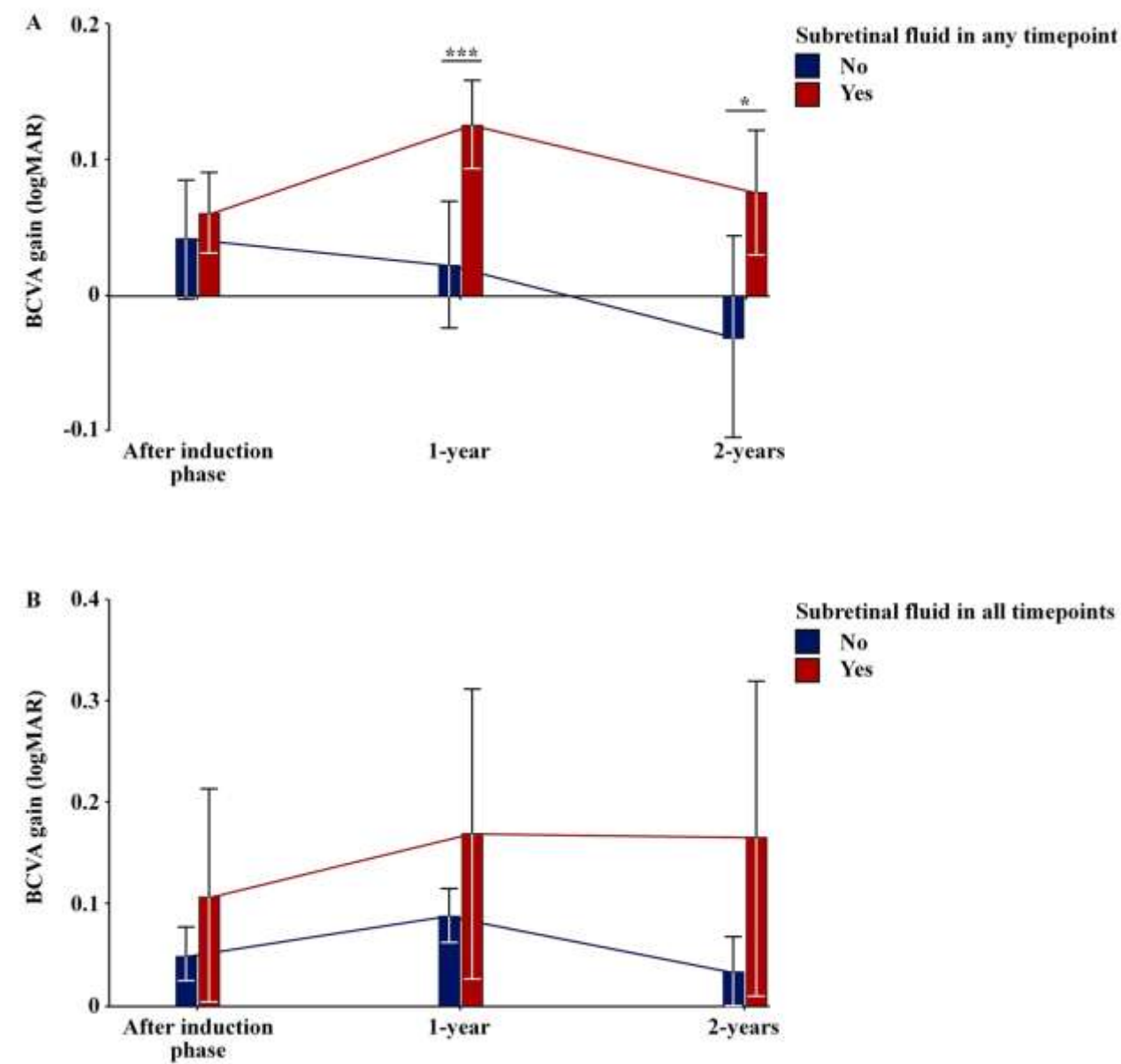
Table 4. Anatomical and functional outcomes in regard subretinal fluid status.

Parameter	Subretinal fluid at any timepoint		P-value
	No	Yes	
BCVA (logMAR)			
Baseline	0.48 ± 0.34	0.53 ± 0.33	<u>0.082</u>
After induction phase	0.44 ± 0.33	0.47 ± 0.32	<u>0.219</u>
1-year	0.42 ± 0.30	0.39 ± 0.25	<u>0.618</u>
2-years	0.45 ± 0.34	0.38 ± 0.27	<u>0.217</u>
CRT (μm)			
Baseline	333 ± 125	430 ± 164	<0.001
After induction phase	270 ± 93	325 ± 92	<0.001
1-year	252 ± 92	283 ± 104	0.005
2-years	229 ± 64	272 ± 88	<0.001

Parameter	Subretinal fluid at all timepoints		P-value
	No	Yes	
BCVA (logMAR)			
Baseline	0.51 ± 0.33	0.54 ± 0.39	<u>0.952</u>
After induction phase	0.46 ± 0.32	0.44 ± 0.28	<u>0.905</u>
1-year	0.40 ± 0.27	0.37 ± 0.28	<u>0.164</u>
2-years	0.40 ± 0.27	0.39 ± 0.24	<u>0.303</u>
CRT (μm)			
Baseline	398 ± 160	397 ± 144	0.964
After induction phase	305 ± 127	341 ± 84	0.203
1-year	269 ± 100	346 ± 97	<0.001
2-years	255 ± 83	303 ± 84	0.014

Data are given as mean ± SD. For two-group comparisons, non-parametric variables were analyzed with the Mann-Whitney U-test and continuous variables with the Student's T-test. Bold = P<0.05.

When analyzing BCVA gain during the treatment, eyes with SRF at any timepoint demonstrated greater improvement compared with eyes without SRF (Online Resource 5). At 1-year, BCVA gain was higher in eyes with SRF (0.13 ± 0.27 vs 0.02 ± 0.26 logMAR units, $P < 0.001$, Online Resource 5), and this difference remained at 2-years (0.07 ± 0.30 vs -0.03 ± 0.31 logMAR units, $P = 0.015$, Online Resource 5).



Discussion

Here, we found that SRF in wet AMD was not associated with worse visual outcomes whereas IRF was consistently associated with poorer visual acuity. These findings suggest that residual SRF may be tolerated without compromising visual prognosis. The role of SRF in the management of wet AMD remains a subject of ongoing debate. While many treatment guidelines emphasize complete retinal drying as a universal goal, accumulating evidence has suggested that SRF may not carry the same negative prognostic significance as IRF. For instance, a *post-hoc* analysis by Core et al. demonstrated that persistent SRF, particularly when present in small amounts, was not associated with worse visual outcomes at 1 and 2 years after adjustment for baseline variables and IRF, with similar BCVA observed in eyes with and without predominantly persistent SRF [16]. The FLUID trial compared a relaxed TER protocol that tolerated SRF up to 200 μm at the foveal center with an intensive TER protocol targeting complete fluid resolution [17]. At 2 years, visual outcomes were non-inferior between the groups, while the relaxed approach required fewer injections and allowed longer treatment intervals [17]. These type of findings support the notion that tolerant strategies towards low levels of SRF may reduce treatment burden without compromising vision.

In routine clinical practice, the TER protocol has become widely used to balance treatment efficacy with treatment burden [18-20]. According to most current practices, the macula has to remain dry of both intra- and subretinal fluids and visual acuity has to be stable for even the first treatment interval extension [18, 20-22]. In other units, such as in our previous RCT for TER protocol optimization, a completely dry macula was not required for treatment interval extension [19]. Mechanistically, SRF can be considered as dynamic rather than static state i.e., as a “river” rather than a “lake”, providing vital factors for the macula and inhibiting macular atrophy in a long-term. Yet, this hypothesis has not been proven. In contrast to subretinal fluid, IRF has repeatedly emerged as a marker of more severe retinal disruption and worse functional prognosis. Multiple studies have shown foveal IRF to be associated with significantly lower visual acuity compared with eyes without IRF, and that this negative effect persists across multiple follow-up points [16,23]. Our results reaffirm these observations, highlighting IRF as a clinically relevant indicator of inadequate disease control.

Despite the studies by Guymer et al. and Core et al. supporting the safety of tolerating small amounts of SRF [16,23], current guidelines and consensus recommendations in many regions continue to advocate achieving a completely dry macula before extending injection intervals [18,

20-22]. This reflects a more conservative school of thought, where any residual fluid is interpreted as ongoing disease activity and a potential risk for long-term structural damage. Emerging evidence from modern anti-VEGF studies suggests a more nuanced interpretation. Studies have shown that patients achieving early and sustained fluid control are more likely to attain extended treatment intervals, highlighting the importance of initial treatment response [24], rather than strict long-term fluid elimination. Similarly, effective fluid control has been associated with improved anatomical outcomes [25]. Importantly, these findings do not necessarily imply that all residual SRF must be eliminated at every time point, but rather support the concept that disease activity should be interpreted dynamically, taking into account both fluid type and overall treatment response. The question of whether SRF should be completely eliminated is not only anatomical but also clinically relevant from a patient-centered perspective. TER protocol aim to balance efficacy with treatment burden, and given the chronic nature of wet AMD and the advanced age of most patients, reducing injection frequency is particularly important. Real-world studies suggest that less frequent injection schedules, such as with TER protocol, are associated with improved patient-reported outcomes and quality of life in wet AMD [26].

This study has several limitations. First, detailed data on injection intervals and cumulative number of anti-VEGF injections were not collected, which may confound the observed associations between SRF and visual outcomes. Second, macular atrophy progression was not assessed to elucidate the proposed hypothesis, and the relatively short two-year follow-up may be insufficient to capture long-term structural changes. Finally, as a real-world observational study, variations in imaging acquisition, follow-up schedules, and treatment decisions may introduce heterogeneity, although they also reflect routine clinical practice. To conclude, while IRF remains a marker of active, vision-threatening disease requiring prompt treatment, our findings emphasize that small and stable amounts of SRF may be tolerated in selected cases. This approach would enable longer treatment intervals without compromising visual outcomes, thereby reducing treatment burden. Future research should aim to confirm these findings in larger cohorts and to define precise SRF thresholds and characteristics that can be safely tolerated.

Declarations

Financial Disclosures: The authors have neither proprietary nor commercial interests in any medications or materials discussed in this study. Dr. Tuuminen is a scientific adviser (advisory board, honoraria) to Alcon Laboratories, Inc., Allergan, Inc., Bayer AG, F. Hoffmann-La Roche Ltd., and Novartis AG, has received payment for expert testimony (Bayer AG), and has received clinical trial support (study medicines) from Bayer AG and Laboratoires Théa.

Conflict of Interests: No conflicting relationships exist for any author.

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Ethics approval: The study was approved by the Medical Research Ethics Committee (THL/587/14.02.00/2025 FD:0074000125), and it adhered to the tenets of the Declaration of Helsinki.

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Figure Legends

Fig. 1. *Representative optical coherence tomography scans of persistent fluid.* Upper line represents persistent intraretinal fluid and lower line persistent subretinal fluid.

Online Resource 1. *Representative optical coherence tomography scans of persistent subretinal fluid.*

Online Resource 5. *Best-corrected visual acuity gain among eyes with and without subretinal fluid.* Data is given as mean $\pm$ 95% confidence interval. Eyes categorized according to the presence of subretinal fluid (A) at any timepoint and (B) at all timepoints. BCVA = best-corrected visual acuity. *= $P < 0.05$; **= $P < 0.001$.