Ophthalmol Ther (2022) 11:1119–1130
https://doi.org/10.1007/s40123-022-00491-1

ORIGINAL RESEARCH

Association Between Visual Acuity and Fluid Compartments with Treat-and-Extend Intravitreal Aflibercept in Neovascular Age-Related Macular Degeneration: An ARIES Post Hoc Analysis

Varun Chaudhary · Frank G. Holz · Sebastian Wolf · Edoardo Midena · Eric H. Souied · Helmut Allmeier · George Lambrou · Tobias Machewitz · Paul Mitchell on behalf of the ARIES study investigators

Received: January 14, 2022 / Accepted: February 22, 2022 / Published online: March 18, 2022

ABSTRACT

Introduction: Recently, there has been growing interest in exploring the relationship between visual acuity and fluid localization in different retinal compartments. This post hoc analysis of the ARIES study explores the relationship between the presence of intraretinal fluid (IRF) and subretinal fluid (SRF), both at baseline and throughout treatment, and best-corrected visual acuity (BCVA) in patients with neovascular age-related macular degeneration (nAMD) treated with intravitreal aflibercept (IVT-AFL) in a treat-and-extend regimen.

Methods: ARIES (NCT02581891) was a multicenter, randomized, phase 3b/4 study comparing the efficacy of two IVT-AFL treat-and-extend regimens over 2 years in patients with treatment-naïve nAMD. This post hoc analysis explores the relationship between the presence of SRF/IRF and absolute BCVA (letter score) at baseline and fixed visits.

Results: In 210 patients (treat-and-extend treatment arms combined), SRF presence at baseline was associated at every time point with

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-022-00491-1.

V. Chaudhary (✉)
Hamilton Regional Eye Institute, St Joseph's Healthcare, Hamilton and Hamilton Health Sciences, 2757 King Street East Room 2500, Hamilton, ON L8G 5E4, Canada
e-mail: vchaudh@mcmaster.ca

F. G. Holz
Department of Ophthalmology, University of Bonn, Bonn, Germany

S. Wolf
Reading Centre and Department for Ophthalmology, Inselspital, University of Bern, Bern, Switzerland

E. Midena
Department of Ophthalmology, University of Padua, Padua, Italy

E. H. Souied
Department d'Ophtalmologie, Hôpital Intercommunal de Créteil, Créteil, France

H. Allmeier · G. Lambrou
Bayer Consumer Care AG, Basel, Switzerland

T. Machewitz
Bayer AG, Berlin, Germany

P. Mitchell
University of Sydney (Westmead Institute for Medical Research), Sydney, NSW, Australia

V. Chaudhary
Division of Ophthalmology, Department of Surgery, McMaster University, Hamilton, ON, Canada

V. Chaudhary
Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada

a numerically higher mean BCVA than if absent, with 10 more letters at week 104. IRF presence at baseline was associated at all but one time point with a numerically lower mean BCVA than if absent (week 104, 8-letter difference). Baseline SRF+IRF was associated with lower BCVA (week 104, 7-letter difference) than if only SRF was present, but higher BCVA (week 104, 8-letter difference) than if only IRF was present. Absence of SRF+IRF was not associated with better BCVA at any time point during the study.

Conclusion: In ARIES, in patients with nAMD treated with IVT-AFL, the presence of SRF was associated with better visual acuity, whereas IRF was associated with poorer visual acuity. The findings of this post hoc analysis suggest that differentiating IRF from SRF may offer better prognostic value in guiding treatment-extension decisions than the use of combined or "any" IRF and SRF. Prospective trials are needed to validate these results and determine their clinical relevance.

Trial registration number (ClinicalTrials.gov): NCT02581891.

Keywords: Aflibercept; Intraretinal Fluid; Neovascular Age-Related Macular Degeneration; Subretinal Fluid; Treat-and-Extend; Visual Acuity

Key Summary Points

Why carry out this study?

Recently, there has been growing interest in exploring how fluid localization in different retinal compartments may offer additional prognostic value to that of central retinal thickness and in elucidating the relationship between visual outcomes, intraretinal fluid (IRF), and subretinal fluid (SRF) in patients with neovascular age-related macular degeneration (nAMD).

This post hoc analysis of the ARIES study is one of the first analyses to evaluate the relationship between retinal fluid status and visual acuity in patients with nAMD who were treated with intravitreal aflibercept in a treat-and-extend regimen in a clinical trial setting.

What was learned from the study?

At baseline and the mandatory study visits, the presence of SRF was associated with better visual acuity, whereas IRF was associated with poorer visual acuity; a "completely dry" retina (neither IRF nor SRF present) was not associated with better visual acuity during the study.

Differentiating IRF from SRF may offer better prognostic value in guiding treatment-extension decisions than the combined use of IRF and SRF.

Further investigations are warranted to validate these findings and explore the mechanisms of action underlying the effects of retinal fluid on visual acuity.

DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.19214331.

INTRODUCTION

Effective suppression of vascular endothelial growth factor (VEGF) is key to optimizing visual acuity outcomes in patients with neovascular age-related macular degeneration (nAMD) [1, 2], and approved anti-VEGF therapies such as intravitreal aflibercept (IVT-AFL) and ranibizumab have become the gold standard in the treatment of nAMD [2]. A proactive, individualized treat-and-extend (T&E) regimen is the current preferred approach over fixed dosing or

the reactive pro re nata (PRN) regimen to maintain improvements in functional and structural outcomes while reducing the monitoring/treatment burden associated with anti-VEGF therapies, particularly over the medium to long term [3–5].

In clinical trials and routine clinical practice, assessments of treatment efficacy and decisions to re-treat or extend the treatment interval in T&E regimens are typically based on changes in anatomic endpoints such as central retinal thickness (CRT), as assessed by optical coherence tomography (OCT) [2, 6, 7]. Recently, there has been growing interest in exploring how fluid localization in different compartments may offer superior prognostic value to that of CRT in elucidating the relationship between visual outcomes, intraretinal fluid (IRF), and subretinal fluid (SRF) [6–9]. However, to date, most analyses of the relationships between retinal fluid status and visual acuity in the management of nAMD have been based on fixed-dose and PRN regimens [10].

The ARIES study (NCT02581891) compared the efficacy and safety of two different T&E regimens of 2 mg IVT-AFL in treatment-naïve patients with nAMD [11]. The treatment regimens comprised early-start T&E (T&E initiated after three initial monthly doses) and late-start T&E (T&E initiated after 1 year of fixed dosing, comprising three initial monthly doses followed by fixed dosing every 8 weeks). The criteria for treatment interval extension included the total absence of IRF and the absence of SRF > 50 μm. The mean best-corrected visual acuity (BCVA) outcomes for the early- and late-start T&E regimens were similar, with one injection difference over 2 years.

The present post hoc analysis describes the relationship between absolute BCVA and retinal fluid compartment status (presence or absence of IRF and/or SRF) at prespecified, mandatory visits in the ARIES study.

METHODS

The ARIES Study

The methods used in the ARIES study (NCT02581891) have been published in detail elsewhere [11]. Briefly, ARIES was a multicenter, randomized, open-label, phase 3b/4 study that compared the efficacy of two different IVT-AFL T&E dosing regimens over 2 years in treatment-naïve patients with nAMD. Eligible patients were aged ≥ 50 years with a baseline BCVA of 25–73 letters and active choroidal neovascularization secondary to age-related macular degeneration with foveal involvement. Patients received three initial monthly doses of 2 mg IVT-AFL (week 0, week 4, and week 8); after a fourth dose at week 16, the patients ($N = 271$) were immediately assigned randomly 1:1 to either the early-start T&E arm (treatment intervals adjusted by 2-week increments to a maximum of 16 weeks provided that all anatomic criteria were met) or the late-start T&E arm (fixed dosing every 8 weeks until week 48, following which the treatment intervals were adjusted by 2-week increments to a maximum of 16 weeks provided that all anatomic criteria were met). Patients who had no IRF or SRF at week 16 (i.e., were "completely dry") received a single 4-week extension of their treatment interval to a total of 12 weeks, with the next visit being scheduled at week 28; from week 28, the normal extension algorithm was applied.

The anatomic criteria for treatment interval extension (based on spectral-domain OCT) were the absence of IRF, absence of new neovascularization or hemorrhage, and SRF ≤ 50 μm in thickness. When these criteria were not met, the treatment interval was reduced to the last effective interval but could be extended again if the criteria were met in subsequent visits. SRF and IRF presence or absence and SRF thickness were assessed by the investigators and confirmed by a central reading center using spectral-domain OCT scans with standardized settings (volume scan, 6.0 mm × 6.0 mm; crosshair scan, 6.0 mm in length with fixation on the macula). Fluid was assessed across the entire macular scan and was not focused on

either the foveal or non-foveal region alone. The proportion of patients with changes in morphologic criteria such as geographic atrophy and their mean BCVA at each time point was not an outcome assessed in the ARIES trial; these criteria were, therefore, not included in this analysis.

The primary endpoint was the mean BCVA change from randomization (week 16) to week 104 in the per-protocol set (PPS). The PPS included all patients in the full analysis set without any major protocol deviations (such as a treatment duration of < 52 weeks, no BCVA assessment at ≥ 52 weeks, or patients who needed injections at shorter intervals than every 2 months between week 16 and week 52). The full analysis set included all randomized patients who received any quantity of the study drug and had a BCVA assessment at week 16 and ≥ 1 BCVA assessment after week 16.

Analysis of Fluid Compartments and BCVA

This post hoc fluid analysis of ARIES included all patients in the PPS, with the early-start and late-start treatment arms combined. The combination of the two treatment arms was based on the findings of the primary analysis of the ARIES study [11]. Similar visual and anatomic outcomes were observed in the two arms, with only one injection difference reported over 2 years of treatment. Only data from the mandatory study visits (baseline and weeks 4, 8, 16 [randomization], 52, and 104) were analyzed here, as the treatment schedules were individualized and the timing of visits varied between patients. Mean absolute BCVA (± standard error of the mean [SEM]) at each mandatory visit throughout the study up to week 104 was calculated for patients grouped by the presence or absence of either IRF or SRF, or both IRF and SRF, at baseline. Mean absolute BCVA (SEM) was also calculated for patients grouped by the presence or absence of either IRF or SRF, or both IRF and SRF, at each mandatory visit up to week 104. Data were analyzed at the level of each fluid category at the specified time points, and the analysis did not follow individual patients across each time point (as the patients included in each category were subject to change over time). Due to the exploratory nature of these analyses, only a descriptive statistical evaluation was conducted and no statistical inferences were made.

This article is based on a previously conducted study (ARIES; NCT02581891) and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Patients and Treatment Exposure

Data regarding overall patient disposition for ARIES, as well as the patients' baseline demographics and disease characteristics, have been published previously [11]. All patients included in the PPS from the ARIES study were included in this fluid analysis ($N = 210$; two treatment arms combined). The number of patients in the different fluid compartment subgroups and their baseline demographics and disease characteristics are shown in Table 1. Of note, $> 90\%$ of patients (193/210) had SRF present at baseline, and the number of patients without SRF was small ($n = 17$). The mean age and sex ratio were similar in the different fluid subgroups. Over the 2-year course of the study, patients in the different fluid subgroups received a similar mean number of injections that ranged from 11.2 ± 2.2 to 13.0 ± 2.3.

BCVA According to Baseline Fluid Status

In patients with SRF at baseline, the mean BCVA was numerically higher at all mandatory study visits than in patients without baseline SRF, with a 10-letter difference at week 104 (Fig. 1a). In patients with IRF at baseline, the mean BCVA was numerically lower at all mandatory study visits than in those without baseline IRF, with an 8-letter difference at week 104 (Fig. 1b). For patients with both SRF and IRF at baseline, the mean BCVA was numerically lower across the study period than in patients with only SRF at

Table 1 Baseline demographics and characteristics (per-protocol set)

	SRF (with or without IRF)		IRF (with or without SRF)		Both SRF + IRF[a]
	Present, *n* = 193	Absent, *n* = 17	Present, *n* = 123	Absent, *n* = 87	Present, *n* = 108
Age, years	75.8 ± 8.7	79.1 ± 9.9	77.3 ± 8.3	74.3 ± 9.3	77.1 ± 7.9
Sex, female, *n* (%)	110 (57.0)	10 (58.8)	71 (57.7)	49 (56.3)	62 (57.4)
BCVA, ETDRS letters	61.2 ± 11.1	55.5 ± 14.3	57.6 ± 12.5	65.2 ± 8.0	58.0 ± 12.1
Median	64.0	61.0	61.0	68.0	60.5
Range	25–73	27–71	25–73	40–73	25–73
CST, μm	462 ± 135	431 ± 119	491 ± 130	415 ± 126	497 ± 131

Values represent the mean ± SD unless otherwise indicated

[a]This subgroup comprised patients in whom both SRF and IRF were simultaneously present at baseline

BCVA best-corrected visual acuity, *CST* central subfield thickness, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IRF* intraretinal fluid, *SD* standard deviation, *SRF* subretinal fluid

baseline (7 fewer letters at week 104; Fig. 1c). The mean BCVA was numerically higher across the study period in patients with both SRF and IRF at baseline than in patients with only IRF at baseline (8 more letters at week 104; Fig. 1c).

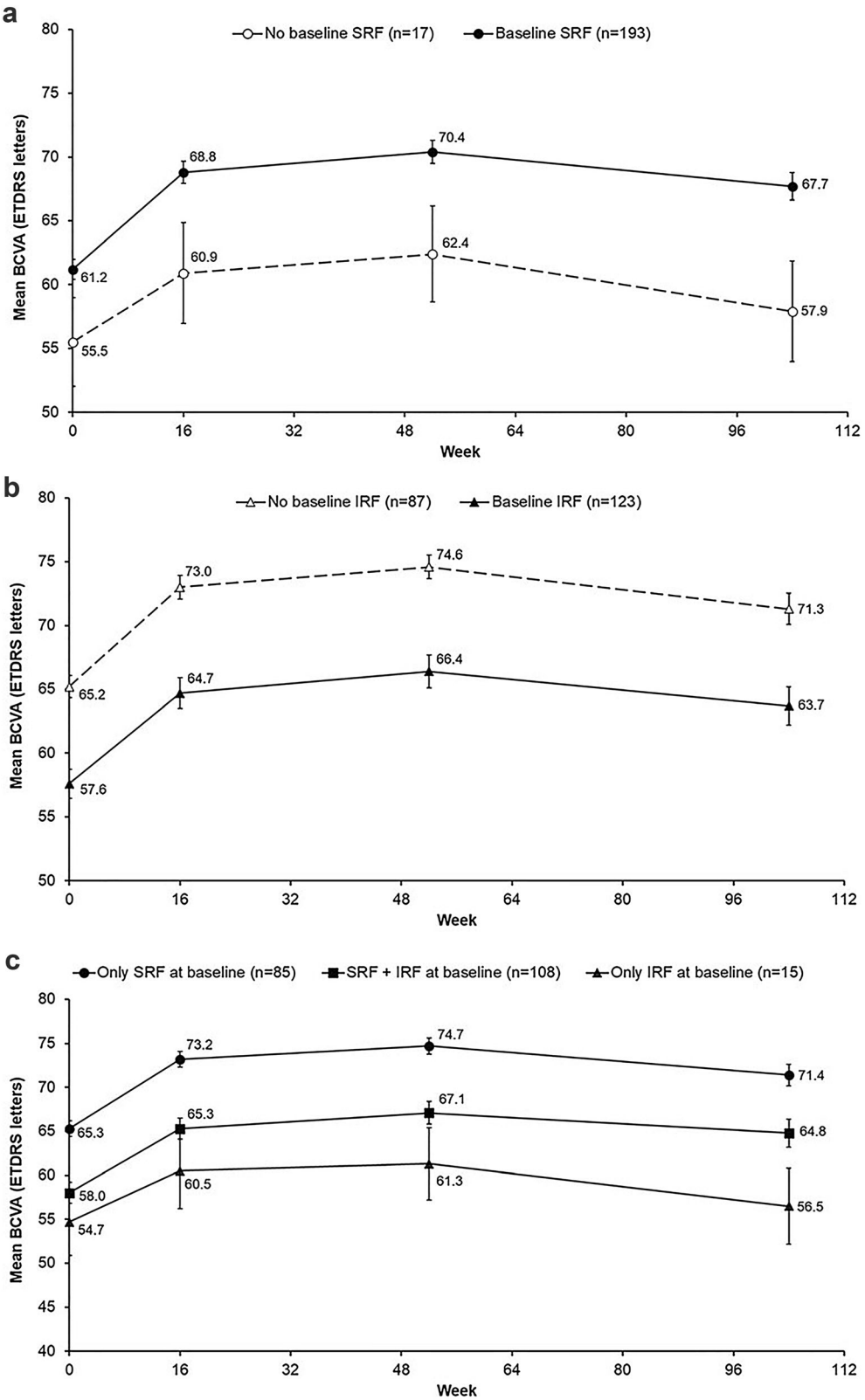
Unadjusted for any differences in baseline BCVA or other potential confounder, the mean ± standard deviation change in BCVA at week 104 from baseline was 2.4 ± 12.5 letters and 6.4 ± 12.8 letters for patients without and with baseline SRF (irrespective of baseline IRF), respectively, and 6.1 ± 10.5 letters and 6.1 ± 14.2 letters for patients without and with baseline IRF (irrespective of baseline SRF), respectively. The mean change in BCVA at week 104 from baseline was 1.8 ± 13.2 letters in patients with only IRF at baseline, 6.0 ± 10.6 letters for those with only SRF at baseline, and 6.7 ± 14.3 letters for those with both SRF and IRF at baseline.

Association Between Fluid Status and BCVA at Mandatory Study Visits

The presence of SRF at each of the mandatory visits was associated with numerically better BCVA than if SRF was absent (Fig. 2a). The presence of IRF was associated at all but one of the mandatory visits with numerically poorer BCVA than if IRF was absent (Fig. 2b). A complete absence of SRF and IRF was not associated with better BCVA at any of the mandatory visits (Fig. 2c). By week 52, one patient had discontinued the study, and by week 104, a further 15 patients had discontinued the study. These patients were not included in the fluid analysis at these time points. Both patients with and without any fluid at week 104 showed improvements in their mean BCVA compared with baseline as a result of IVT-AFL treatment (Fig. 2c).

DISCUSSION

This post hoc analysis of the ARIES study aimed to evaluate the relationship between visual acuity and the presence of IRF and SRF in patients with nAMD treated with IVT-AFL T&E. The presence of SRF at baseline was associated with better visual acuity over the 2-year study period, whereas the presence of IRF at baseline was associated with worse visual acuity over this period. Similarly, the post-baseline presence of residual SRF was associated with better visual acuity at each time point, whereas the presence of residual IRF was associated with worse visual acuity. Importantly, although both patients


a
No baseline SRF (n=17)
Baseline SRF (n=193)
Mean BCVA (ETDRS letters)
Week
68.8
70.4
67.7
61.2
60.9
62.4
57.9
55.5
b
No baseline IRF (n=87)
Baseline IRF (n=123)
Mean BCVA (ETDRS letters)
Week
73.0
74.6
71.3
65.2
64.7
66.4
63.7
57.6
c
Only SRF at baseline (n=85)
SRF + IRF at baseline (n=108)
Only IRF at baseline (n=15)
Mean BCVA (ETDRS letters)
Week
73.2
74.7
71.4
65.3
65.3
67.1
64.8
58.0
60.5
61.3
56.5
54.7

◀**Fig. 1** Mean absolute BCVA by presence/absence of baseline **a** SRF (with or without IRF), **b** IRF (with or without SRF), or **c** IRF only, SRF only, or SRF plus IRF at the mandatory study visits. Values represent the mean ± SEM. *BCVA* best-corrected visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IRF* intraretinal fluid, *SEM* standard error of the mean, *SRF* subretinal fluid

with and without any fluid showed improvements in their mean BCVA over the study period, a "completely dry" retina (neither IRF nor SRF present) was not associated with better visual acuity at any time point.

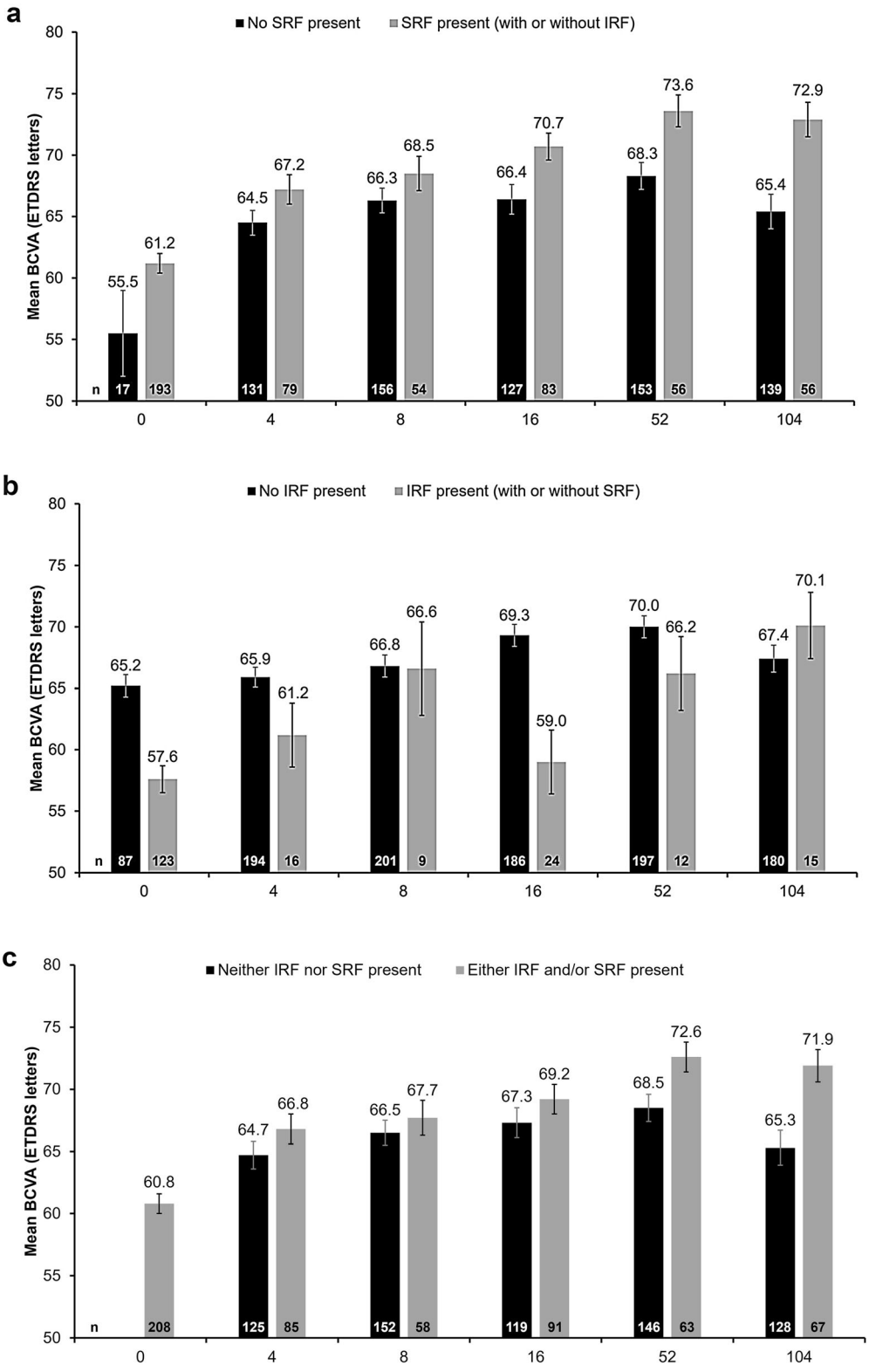
The phase 3 HARBOR clinical trial evaluated the efficacy and safety of ranibizumab in 1097 patients with treatment-naïve nAMD [12], and a post hoc analysis of HARBOR investigated the relationship between retinal fluid and vision outcomes in 917 of the patients aged ≥ 50 years with subfoveal nAMD associated with SRF and/or IRF at baseline, screening, or week 1 (all treatment arms pooled) [13]. The analysis indicated that the presence of residual SRF at months 12 and 24 was associated with higher baseline BCVA compared with resolved SRF. They further found that residual SRF in the absence of IRF resulted in the largest mean BCVA gains (adjusted for baseline BCVA) of all the groups stratified by fluid status, with the poorest vision outcomes being observed in eyes with residual IRF. The authors concluded that the evaluation of residual fluid in nAMD during anti-VEGF treatment should be more nuanced than determining whether the macula is wet or dry. The aim of the present ARIES analysis was to evaluate the potential impact of fluid on absolute BCVA. We did not evaluate the impact of fluid on the magnitude of BCVA gains following treatment, and the mean changes in BCVA for patients in the baseline fluid categories are given for information purposes only and not adjusted for baseline BCVA. No statistical inferences were made.

Newer imaging technologies, particularly advances in OCT imaging, are now enabling more detailed analyses of the structures within the retina, and investigations are ongoing to determine their potential as structural criteria to guide personalized treatment [6, 9]. However, current treatment guidelines do not always provide sufficient guidance regarding the differentiation of retinal fluid types and how these OCT findings should be interpreted [2, 6, 9]. Several studies have indicated the importance of IRF and SRF as prognostic markers of visual outcomes in nAMD, but there have been few prospective studies, with the notable exception of FLUID [14] and CATT [15], evaluating the effect of fluid status on visual outcomes. Instead, the majority of evidence has emerged from post hoc and exploratory analyses of various randomized controlled trials. Further, a recent systematic literature review extracted data from both randomized clinical trials and observational studies on the impact of fluid compartments on functional outcomes in nAMD [10].

Consistent with the findings of this post hoc analysis, past studies have observed a negative correlation between IRF and visual acuity, with a similarly negative impact being observed for intraretinal cysts [10, 13, 15–22]. Although there is agreement across the medical and research communities that there is a negative effect of IRF on visual acuity, further research is required to elucidate the contributing pathophysiologic mechanisms. Certainly, IRF appears to be associated with increased levels of macular atrophy and photoreceptor impairment [23], the latter possibly as a result of Müller cell dysfunction [24].

The relationship between SRF and visual acuity has been less clear; whereas several studies have suggested that the presence of some SRF is at least well tolerated [14, 21], other studies have reported that baseline and stable residual SRF are associated with better visual acuity [13, 15, 16, 18, 19]. A systematic literature review on the role of fluid compartments found that treatment regimens tolerating the presence of stable SRF (but not IRF) may lead to improved visual outcomes in nAMD [10].

A recent post hoc analysis of the OCTAVE study illustrated the potential impact of SRF, specifically within the ellipsoid zone (EZ) [23]. In this analysis, EZ integrity was found to be correlated with better BCVA at all time points


a
No SRF present
SRF present (with or without IRF)
Mean BCVA (ETDRS letters)
80
75
70
65
60
55
50
55.5
61.2
64.5
67.2
66.3
68.5
66.4
70.7
68.3
73.6
65.4
72.9
n
17
193
131
79
156
54
127
83
153
56
139
56
0
4
8
16
52
104
b
No IRF present
IRF present (with or without SRF)
Mean BCVA (ETDRS letters)
65.2
57.6
65.9
61.2
66.8
66.6
69.3
59.0
70.0
66.2
67.4
70.1
n
87
123
194
16
201
9
186
24
197
12
180
15
0
4
8
16
52
104
c
Neither IRF nor SRF present
Either IRF and/or SRF present
Mean BCVA (ETDRS letters)
60.8
64.7
66.8
66.5
67.7
67.3
69.2
68.5
72.6
65.3
71.9
n
208
125
85
152
58
119
91
146
63
128
67
0
4
8
16
52
104

◀**Fig. 2** Mean absolute BCVA by presence/absence of **a** SRF (with or without IRF), **b** IRF (with or without SRF), or **c** either IRF and/or SRF at each mandatory visit. Values represent the mean ± SEM. *BCVA* best-corrected visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IRF* intraretinal fluid, *SEM* standard error of the mean, *SRF* subretinal fluid

across the 12-month treatment period, and baseline SRF was associated with increased EZ integrity at month 12. Interestingly, EZ integrity was preserved in areas containing residual SRF, whereas the resolution of SRF was associated with areas of EZ impairment, indicating a possible protective role of SRF.

There are several hypotheses regarding a potential protective role of SRF in nAMD, including the following: SRF may provide a spatial buffer between the photoreceptors and toxic metabolites within the diseased retinal pigment epithelium [16, 23]; SRF may help to maintain the photoreceptor alignment necessary for photoreceptor signaling [23]; SRF may help provide trophic support to the overlying retina [16]; and SRF may contain neuroprotective molecules that promote the integrity of the retinal pigment epithelium [16]. It has also been suggested that, for some patients, SRF may be a biomarker of a more benign form of nAMD associated with type 1 macular neovascularization [25]. At present, however, there is no consensus regarding the volume of SRF that can be tolerated. The FLUID study stipulated SRF < 200 μm for treatment interval extension [14], whereas the ongoing TOLERANT study (NCT02550002) is evaluating the use of either no SRF or SRF ≤ 100 μm in the central subfoveal field among the anatomic criteria for interval extension. In the ARIES study, the presence of SRF ≤ 50 μm was used as an anatomic criterion for this purpose.

This is one of the first analyses to evaluate the relationship between retinal fluid status and visual acuity in nAMD treated with T&E IVT-AFL in a clinical trial setting. However, it should be acknowledged that the effects of other factors such as baseline BCVA, disease duration, EZ integrity, atrophy, and the volume of SRF and IRF were not assessed in this analysis, only the presence or absence of these retinal fluids. Furthermore, the presence or absence of subretinal pigment epithelium fluid and the impact on BCVA was not assessed, nor was the impact of fluid status on functional outcomes. As this was a post hoc analysis performed as a hypothesis-generating exercise, it was not designed or powered to detect statistical significance or to investigate the effects of additional factors. Performing multiple subgroup analyses on a dataset is known to carry the risk of generating spurious results [26], and we, therefore, focused on one factor here, namely the impact of fluid in the retinal compartments on BCVA. Finally, several of the fluid subgroups were relatively small, and 15 patients discontinued at week 104; this may limit the interpretation of these results. Overall, this post hoc analysis reveals interesting observations that are supported by previous studies but should be validated in prospective trials.

CONCLUSIONS

In ARIES, IVT-AFL T&E was shown to be effective in reducing fluid and improving vision in treatment-naïve nAMD eyes regardless of fluid status. This post hoc analysis of ARIES indicated that the presence of SRF was associated with better visual acuity at baseline and consistently higher visual acuity over the treatment period compared with the absence of SRF. In contrast, the presence of IRF was generally associated with worse visual acuity, as was the complete absence of IRF and SRF. These findings suggest that the role of the fluid compartments should be considered, and the use of combined or "any" SRF and IRF as a surrogate marker to guide IVT-AFL treatment-extension decisions should be reevaluated. Instead, elimination of IRF should be considered key by clinicians using proactive treatment regimens, as residual SRF may play a role in preserving visual function, which emerging evidence from other studies is also indicating. Further investigations are needed to fully elucidate the mechanisms of action underlying the effect of IRF and SRF on visual acuity and to determine the clinical relevance

thereof in the progression and treatment of nAMD.

ACKNOWLEDGEMENTS

The authors thank all the patients and investigators who participated in the ARIES study.

Funding. The ARIES study was sponsored by Bayer AG, Leverkusen, Germany. Bayer Consumer Care AG, Basel, Switzerland funded the post hoc analysis and is also responsible for funding the journal's Rapid Service Fees.

Medical Writing and Editorial Assistance. Medical writing and editorial support for the preparation of this manuscript, under the guidance of the authors, was provided by Natasha Beeton-Kempen, ApotheCom, UK, and was funded by Bayer Consumer Care AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP3) guidance (Ann Intern Med. 2015;163:461–464).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study conception, design, and interpretation of the results. Helmut Allmeier, George Lambrou, and Tobias Machewitz performed the data curation and analyses. All authors provided critical review of the manuscript, and all authors read and approved the final manuscript.

Prior Presentation. The Association for Research in Vision and Ophthalmology (ARVO) Virtual Meeting, 1–7 May, 2021; the Canadian Ophthalmological Society (COS) Virtual Meeting, 24–27 June, 2021; the Retinologische Gesellschaft, Munich, Germany, 25–26 June, 2021; and the European Society of Retina Specialists (EURETINA) Virtual Meeting, September 9–12, 2021.

Disclosures. Varun Chaudhary has received funding from Allergan Inc., Bayer Healthcare, and Novartis Pharma AG; and has received consulting fees from Alcon Laboratories, Bayer Healthcare, Novartis Pharma AG, and Roche. Frank G. Holz has served as a Steering Committee member for Bayer; has served as a consultant for Acucela, Apellis Pharmaceuticals, Bayer, Bioeq/Formycon AG, Boehringer Ingelheim, Chengdu Kanghong Pharmaceuticals, Geuder AG, Graybug Vision, Heidelberg Engineering, Lin Bioscience, Novartis, Oxurion, Pixium Vision, Roche/Genentech, and Stealth BioTherapeutics; has received research support from Acucela, Apellis Pharmaceuticals, Bayer, Bioeq/Formycon AG, CenterVue, Chengdu Kanghong Pharmaceuticals, Heidelberg Engineering, NightstaRx, Novartis, Optos, Pixium Vision, Roche/Genentech, and Zeiss Pharma; and has received honoraria or travel reimbursement from Acucela, Apellis Pharmaceuticals, Bayer, Ellex, Graybug Vision, Heidelberg Engineering, Lin Bioscience, Novartis, Oxurion, Pixium Vision, Roche/Genentech, Stealth BioTherapeutics, and Zeiss Pharma. Edoardo Midena has served as a Steering Committee member for Bayer. Eric Souied has served as a Steering Committee member for Bayer. Sebastian Wolf has served as a Steering Committee member for Bayer; has served as a consultant for Allergan, Bayer, Boehringer Ingelheim, Chengdu Kanghong Biotech, Heidelberg Engineering, Novartis, Oxurion, Roche, and Zeiss; and has received grant support from Heidelberg Engineering. Paul Mitchell has served as a Steering Committee member for Bayer and has received consulting fees from Allergan, Bayer, and Novartis. Helmut Allmeier and George Lambrou are employees of Bayer Consumer Care AG, Basel, Switzerland, and Tobias Machewitz is an employee of Bayer AG, Berlin, Germany.

Compliance with Ethics Guidelines. This article is based on a previously conducted study (ARIES; NCT02581891) and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available. Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing." This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers' patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

REFERENCES

1. Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. Neuron. 2012;75(1):26–39.

2. 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(9):1144–67.

3. Freund KB, Korobelnik J, Devenyi R, et al. Treat-and-extend regimens with anti-VEGF agents in retinal diseases: a literature review and consensus recommendations. Retina. 2015;35(8):1489–506.

4. Patel PJ, Devonport H, Sivaprasad S, et al. Aflibercept treatment for neovascular AMD beyond the first year: consensus recommendations by a UK expert roundtable panel, 2017 update. Clin Ophthalmol. 2017;11:1957–66.

5. Lanzetta P, Loewenstein A, Vision Academy Steering Committee. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. Graefes Arch Clin Exp Ophthalmol. 2017;255(7):1259–73.

6. Kodjikian L, Parravano M, Clemens A, et al. Fluid as a critical biomarker in neovascular age-related macular degeneration management: literature review and consensus recommendations. Eye (Lond). 2021;35(8):2119–35.

7. Kaiser PK, Wykoff CC, Singh RP, et al. Retinal fluid and thickness as measures of disease activity in neovascular age-related macular degeneration. Retina. 2021;41(8):1579–86.

8. Moraes G, Fu DJ, Wilson M, et al. Quantitative analysis of OCT for neovascular age-related macular degeneration using deep learning. Ophthalmology. 2021;128(5):693–705.

9. 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.

10. Chaudhary V, Matonti F, Zarranz-Ventura J, Stewart MW. The impact of fluid compartments on functional outcomes for patients with neovascular age-related macular degeneration: a systematic literature review. Retina. 2021. https://doi.org/10.1097/IAE.0000000000003283 (**published online ahead of print**).

11. Mitchell P, Holz FG, Hykin P, et al. Efficacy and safety of intravitreal aflibercept using a treat-and-extend regimen for neovascular age-related macular degeneration: the ARIES study: a randomized clinical trial. Retina. 2021;41(9):1911–20.

12. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology. 2014;121(11):2181–92.

13. Holekamp NM, Sadda S, Sarraf D, et al. Effect of residual retinal fluid on visual function in ranibizumab-treated neovascular age-related macular degeneration. Am J Ophthalmol. 2022;233:8–17.

14. 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: FLUID study 24-month results. Ophthalmology. 2019;126(5):723–34.

15. 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(4):865–75.

16. Jaffe GJ, Ying GS, Toth CA, et al. Macular morphology and visual acuity in year five of the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2019;126(2):252–60.

17. Ritter M, Simader C, Bolz M, et al. Intraretinal cysts are the most relevant prognostic biomarker in neovascular age-related macular degeneration independent of the therapeutic strategy. Br J Ophthalmol. 2014;98(12):1629–35.

18. Schmidt-Erfurth U, Vogl WD, Jampol LM, Bogunovic H. Application of automated quantification of fluid volumes to anti-VEGF therapy of neovascular age-related macular degeneration. Ophthalmology. 2020;127(9):1211–9.

19. Schmidt-Erfurth U, Waldstein SM, Deak GG, Kundi M, Simader C. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. Ophthalmology. 2015;122(4):822–32.

20. Simader C, Ritter M, Bolz M, et al. Morphologic parameters relevant for visual outcome during anti-angiogenic therapy of neovascular age-related macular degeneration. Ophthalmology. 2014;121(6):1237–45.

21. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. Ophthalmology. 2016;123(7):1521–9.

22. Waldstein SM, Wright J, Warburton J, Margaron P, Simader C, Schmidt-Erfurth U. Predictive value of retinal morphology for visual acuity outcomes of different ranibizumab treatment regimens for neovascular AMD. Ophthalmology. 2016;123(1):60–9.

23. Riedl S, Cooney L, Grechenig C, et al. Topographic analysis of photoreceptor loss correlated with disease morphology in neovascular age-related macular degeneration. Retina. 2020;40(11):2148–57.

24. Bringmann A, Wiedemann P. Muller glial cells in retinal disease. Ophthalmologica. 2012;227(1):1–19.

25. Siedlecki J, Fischer C, Schworm B, et al. Impact of sub-retinal fluid on the long-term incidence of macular atrophy in neovascular age-related macular degeneration under treat and extend anti-vascular endothelial growth factor inhibitors. Sci Rep. 2020;10(1):8036.

26. Farrokhyar F, Skorzewski P, Phillips MR, et al. When to believe a subgroup analysis: revisiting the 11 criteria. Eye (Lond). 2022. https://doi.org/10.1038/s41433-022-01948-0 (**published online ahead of print**).