IMPACT OF FLUID COMPARTMENTS ON FUNCTIONAL OUTCOMES FOR PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

A Systematic Literature Review

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Purpose: Understanding the impact of fluid in different retinal compartments is critical to developing treatment paradigms that optimize visual acuity and reduce treatment burden in neovascular age-related macular degeneration. This systematic review aimed to determine the impact of persistent/new subretinal fluid, intraretinal fluid, and subretinal pigment epithelial fluid on visual acuity over 1 year of treatment.

Methods: Publication eligibility and data extraction were conducted according to Cochrane methods: 27 of the 1,797 screened records were eligible.

Results: Intraretinal fluid negatively affected visual acuity at baseline and throughout treatment, with foveal intraretinal fluid associated with lower visual acuity than extrafoveal intraretinal fluid. Some studies found that subretinal fluid (particularly subfoveal) was associated with higher visual acuity at Year 1 and longer term, and others suggested subretinal fluid did not affect visual acuity at Years 1 and 2. Data on the effects of subretinal pigment epithelial fluid were scarce, and consensus was not reached. Few studies reported numbers of injections associated with fluid status.

Conclusion: To optimally manage neovascular age-related macular degeneration, clinicians should understand the impact of fluid compartments on visual acuity. After initial treatment, antivascular endothelial growth factor regimens that tolerate stable subretinal fluid (if visual acuity is stable/improved) but not intraretinal fluid may enable patients to achieve their best possible visual acuity. Confirmatory studies are required to validate these findings.

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Treatment of neovascular age-related macular degeneration (nAMD) is based on signs of disease activity, including change in visual acuity, new hemorrhage, increased macular thickness, new/persistent fluid, and evidence of membrane leakage/growth. Fluid seen on optical coherence tomography is an important surrogate marker for disease activity, usually mandating aggressive treatment with intravitreal vascular endothelial growth factor (VEGF) inhibitors.1–5 The introduction of spectral-domain optical coherence tomography and swept-source optical coherence tomography made it possible to detect small anatomic changes within the retina, and thus clinicians can precisely identify fluid within the various retinal compartments.1

Emerging evidence suggests disconnection between morphologic features of the macula, and visual acuity outcomes in patients with nAMD.1,6–12 The presence and location of macular fluid within the intraretinal, subretinal, and subretinal pigment epithelial (sub-RPE) compartments may determine visual acuity outcomes in patients receiving long-term anti-VEGF therapy.10,13,14 However, the relationship between retinal fluid status and VA outcomes is not well understood.
This systematic review aims to determine the impact of persistent and/or new subretinal fluid (SRF), intraretinal fluid (IRF), and sub-RPE fluid on VA outcomes both at baseline and over a 1-year treatment course.

Methods

This review was conducted in accordance with the Cochrane approach. Methods and results are presented according to PRISMA (http://www.prisma-statement.org).

The primary aim was to determine the impact of SRF, IRF, and sub-RPE fluid on VA at Year 1 in patients with nAMD treated with anti-VEGF drugs. Secondary aims were to determine the impact of SRF, IRF, and sub-RPE fluid on VA at other time points, morphologic outcomes, treatment burden, and safety.

The PICOS framework (Table 1) was used to develop search strategies based on disease area, disease-modifying factors, interventions, and study types for EMBASE and PubMed: January 1, 2006, to August 1, 2020 (see Table 1, Supplemental Digital Content 1, http://links.lww.com/IAE/B511). A similar approach was used for CENTRAL (Cochrane Library), World Health Organization International Clinical Trials Registry Platform, the Cumulative Index to Nursing and Allied Health Literature, ClinicalTrials.gov, and OpenGrey. Manual searches of abstracts from recent key conferences (see Table 2, Supplemental Digital Content 1, http://links.lww.com/IAE/B511) were reviewed. Outcomes in patients with nAMD undergoing intravitreal anti-VEGF treatment, stratified by SRF or IRF, were included. Study exclusion criteria are reported in Supplemental Digital Content 1 (see Table 3, http://links.lww.com/IAE/B511).

Titles and/or abstracts of retrieved studies were screened independently by two reviewers to identify those meeting inclusion criteria. The full texts of identified studies were assessed in detail; disagreement over a study’s eligibility was resolved through discussion with a third reviewer. Data (patient baseline demographics and characteristics, number of patients, intervention, protocol, previous treatment [if applicable], type of outcome measure, VA according to fluid and fluid compartment presence/absence, and time point) were extracted to a standardized, prepiloted form for evidence synthesis.

Studies were assessed using the Cochrane risk of bias (RoB-2) tool for randomized controlled trials (see Table 4, Supplemental Digital Content 1, http://links.lww.com/IAE/B511) and the ROBINS-I tool for observational studies (see Table 5, Supplemental Digital Content 1, http://links.lww.com/IAE/B511). Each potential source of bias was judged as conferring low, unclear, or high risk of bias.

Results

Study Selection and Characteristics

After screening 1,797 titles and abstracts, 188 records were judged to be “potentially relevant”; 161 full-text records were excluded (per exclusion criteria) and 27 unique records were reviewed (Figure 1).

Table 2 summarizes results from studies that reported VA over time or change in VA from baseline stratified by presence or absence of SRF and/or IRF.
Functional Outcomes at Year 1

Randomized studies. In a post hoc analysis of the EXCITE trial, baseline SRF was identified as a key predictor of favorable best-corrected visual acuity (BCVA) gains at 1 year \((P = 0.05)\).\(^6\) Best-corrected visual acuity and central retinal thickness only correlated strongly at baseline.

In the CATT trial, in patients with nAMD treated with ranibizumab or bevacizumab, baseline IRF, SRF, and sub-RPE fluid were significantly associated with 1-year visual acuity outcomes in univariate analysis, but not in multivariate analysis after adjustment for baseline variables.\(^{16}\)

In a post hoc analysis of the CATT trial,\(^{13}\) IRF negatively affected vision at all evaluated time points within the first year of treatment, particularly when there was foveal involvement. Visual acuity in eyes with foveal IRF was two lines lower than in those without fluid and one line lower than in eyes with

| Table 1. Population, Intervention, Comparison, Outcome, and Setting (PICOS) |
|---------------------------------------------------------------|
| **Item** | **Search Details** |
| Population | Disease Neovascular age-related macular degeneration |
| Intervention | Anti-VEGF therapy Afibercept, ranibizumab, bevacizumab, brolucizumab, abicipar used in patients with SRF and/or IRF at defined time points |
| Comparison | Anti-VEGF therapy Afibercept, ranibizumab, bevacizumab, brolucizumab, abicipar used in patients with no SRF and/or IRF at defined time points |
| Outcome | Primary: Functional outcomes at Year 1 Visual acuity, OCT data, CNV type (1–3 or PCV), fibrosis, RPE atrophy, macular atrophy, RPE detachment, vascular proliferation, treatment burden (number of injections and clinic visits), patient quality of life, uveitis, and safety |
| | Secondary: Functional outcomes at other time points, morphologic outcomes, treatment burden, and safety |
| Setting | Study design Randomized and observational studies |
| | CNV, choroidal neovascularization; IRF, intraretinal fluid; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; RPE, retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor. |

**Fig. 1.** PRISMA flow diagram.
| Ref                        | Study Design | Bias Risk | Treatment/Protocol                  | Previous Treatment          | N     |
|----------------------------|--------------|-----------|-------------------------------------|-----------------------------|-------|
| Chatziralli et al 2016     | Interventional | Low       | AFL Fixed dose PRN                   | Treatment-naive             | 431   |
| Ebneter et al 2015         | Observational | Mod       | RAN Monthly PRN                       | Treatment-naive             | 31    |
| Ersoy et al 2014           | Observational | Mod       | RAN or BEV Physician discretion PRN  | Treatment-naive             | 30    |
| Dervenis and Younis 2016   | Observational | Low       | RAN PRN Mix                          | Treatment-naive             | 62    |
| Chakravarthy et al 2020    | Observational | Low       | Mixed                                | Mixed previous anti-VEGF    | 321   |
| de Massougnes et al 2018   | Observational | Low       | RAN or AFL Mixed                     | Treatment-naive             | 104   |
| Inan et al 2019            | Observational | Low       | RAN PRN Mix                          | Treatment-naive             | 65    |
| Jaffe et al 2016 (VIEW 1 and 2) | RCT post hoc | Low       | RAN or AFL Q4W (RAN4/AFL4) or Q8W (AFL8) | Treatment-naive             | 1,815 |
| Jaffe et al 2013 (CATT)    | RCT post hoc | Low       | RAN or BEV Monthly or PRN PRN        | Treatment-naive             | 1,185 |
| Kodjikian et al 2018       | RCT post hoc | Low       | RAN or BEV PRN                       | Not reported                | 404   |
| Lin et al 2020             | Observational | Low       | BEV or RAN PRN                       | Treatment-naive             | 77    |
| Ogasawara et al 2018       | Observational | Low       | AFL Fixed RAN PRN                    | Treatment-naive             | 107   |
| Pokroy et al 2018          | Observational | Mod       | BEV PRN Mix                          | Treatment-naive             | 73    |
| Regillo et al 2015 (HARBOR) | RCT          | Low       | Monthly or PRN RAN or RAN + PDT PRN  | Treatment-naive             | 500   |
| Ritter et al 2014 (MONT BLANC) | RCT          | NI        | Monthly or PRN RAN or PRN            | Treatment-naive             | 255   |
| Waldstein et al 2016       | RCT post hoc | Low       | RAN or AFL Q4W (RAN4/AFL4) or Q8W (AFL8) | Treatment-naive             | 1,815 |
| Waldstein et al 2016 (VIEW 1 and 2) | RCT post hoc | Low       | RAN                                 | Treatment-naive             | 353   |
| Waldstein et al 2016 (EXCITE) | RCT post hoc | Low       | RAN or BEV Monthly or quarterly PRN  | Treatment-naive             | 214   |
| Wickremasinghe et al 2012  | Interventional | NI        | RAN or BEV PRN                       | Treatment-naive             | 103   |
| Wickremasinghe et al 2016  | Observational | Mod       | RAN or BEV T&E                       | Treatment-naive             | 35    |
| Kim et al 2017             | Observational | Mod       | RAN or BEV N/A                       | Treatment-naive             | 1,095 |
| Schmidt-Erfurth et al 2020 (HARBOR) | RCT post hoc | Low       | RAN Monthly or PRN                   | Treatment-naive             |       |
Table 2. (Continued)

| Ref                           | Study Design | Bias Risk | Treatment/Protocol                  | Previous Treatment | N    |
|-------------------------------|--------------|-----------|-------------------------------------|--------------------|------|
| Sharma et al 2016<sup>14</sup> (CATT) | RCT          | Low       | RAN or BEV Monthly or PRN            | Treatment-naive    | 1,185|
| Ying et al 2014<sup>9</sup> (CATT)       | RCT          | Low       | RAN or BEV Monthly or PRN            | Treatment-naive    | 1,030|
| Shin et al 2013<sup>39</sup>     | Observational| Low       | Mixed                              | Mixed              | 20   |
| Gianniou et al 2015<sup>40</sup> | Observational| Low       | RAN Q4W                            | Persistent SRF or IRF | 76 eyes |
| Guymer et al 2019<sup>11</sup>   | RCT post hoc | Low       | RAN T&E                           | Treatment-naive    | 349  |
| NCT01972789                    | Observation  | Low       | Monthly                            | Treatment for ≥12 months | 44 (45 eyes) |
| Jang et al 2015<sup>41</sup>    | RCT          | Low       | RAN or BEV Monthly or PRN           | Treatment-naive    | 523  |
| Jaffe et al 2019<sup>10</sup> (CATT) | RCT          | Low       | RAN or BEV Monthly or PRN           | Treatment-naive    | 647  |
| Ying et al 2018<sup>21</sup> (CATT) | RCT          | Low       | RAN or BEV Monthly or PRN           | Treatment-naive    | 523  |

| Ref                           | Outcome                  | No Fluid       | SRF                  | IRF                  | Both SRF and IRF   | Key Points                                                                 |
|-------------------------------|--------------------------|----------------|----------------------|----------------------|-------------------|-----------------------------------------------------------------------------|
| Chatziralli et al 2016<sup>27</sup> | ETDRS letters (by presence of fluid at BL) | BL: 63.2 ± 13.5 | BL: 70.8 ± 12.3 | BL: 61.2 ± 17.3 | BL: 59.6 ± 15.4 | At 12 months: No significant increase in VA from BL prog risk factors: age, increased CST, IRF, PED, subfoveal thickening |
|                              | (by presence of fluid at BL) | Week 8: 61.9 ± 14.0 | Week 8: 70.7 ± 14.1 | Week 8: 59.3 ± 16.6 | Week 8: 60.4 ± 16.6 | Neither BL nor improvement of BCVA at Month 3 was statistically significant between the groups |
|                              |                          | Week 16: 62.3 ± 14.7 | Week 16: 70.9 ± 12.8 | Week 16: 59.2 ± 18.1 | Week 16: 60.6 ± 16.3 |                                                                            |
|                              |                          | Week 24: 61.0 ± 16.1 | Week 24: 70.1 ± 13.3 | Week 24: 60.4 ± 16.6 | Week 24: 62.2 ± 17.1 |                                                                            |
|                              |                          | Week 48: 62.3 ± 17.2 | Week 48: 71.0 ± 12.8 | Week 48: 59.8 ± 17.7 | Week 48: 60.6 ± 17.7 |                                                                            |
|                              |                          |                | P = 0.900 vs. no fluid | P = 0.049 vs. no fluid | P < 0.001 vs. no fluid |                                                                            |
| Ebneter et al 2015<sup>36</sup> | Change in BCVA (ETDRS letters) | N/A            | BL: 59.4 ± 13.3 | BL: 50.0 ± 10.8 | BL: 46.4 ± 18.4 | At 12 months: No significant increase in VA from BL prog risk factors: age, increased CST, IRF, PED, subfoveal thickening |
|                              |                          | 3 months: 65.2 ± 9.1 | 3 months: 55.3 ± 10.0 | 3 months: 54.0 ± 14.1 |                                                                            |
| Ref                          | Outcome                                                                 | No Fluid                                                                 | SRF                                                                 | IRF                                                                 | Both SRF and IRF | Key Points                                                                                                                                 |
|------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Ersoy et al 2014[^32]        | Change in logMAR BCVA per response                                      | Response defined as absence of IRF or SRF at any visit.                  | Nonresponse defined as persistent SRF at all visits.                | N/A                                                                | N/A             | Mean follow-up of 40.25 ± 13.5 months. Eyes with SD-OCT phenotype + isolated PED and SRF often nonresponsive to anti-VEGF, different mechanism may be involved vs. AMD. |
|                              |                                                                         | After 3 injections: −0.07 ± 0.23                                         | After 3 injections: −0.06 ± 0.17 (P = 0.657 vs. response)            | At last visit: 0.07 ± 0.32                                         |                 |                                                                                                                                             |
|                              |                                                                         | At last visit: 0.07 ± 0.32                                                | At last visit: 0.08 ± 0.30 (P = 1.0 vs. response)                     |                                                                     |                 |                                                                                                                                             |
| Dervenis and Younis 2016[^24] | Mean ± SD ETDRS letters                                                 | No SRF                                                                   | BL: 0.59 ± 0.30                                                      | BL: 0.63 ± 0.30                                                     | N/A             | PED at presentation was associated with lower CMT. RPE disruption was associated with worse VA at Month 6. IRF presence was associated with worse VA at Month 4. |
|                              |                                                                         | BL: 0.62 ± 0.26                                                          | Month 4: 0.42 ± 0.39                                                 | Month 4: 0.62 ± 0.47                                               |                 |                                                                                                                                             |
|                              |                                                                         | Month 6: 0.65 ± 0.53                                                     | Month 6: 0.48 ± 0.36                                                 | Month 6: 0.57 ± 0.45                                               |                 |                                                                                                                                             |
|                              |                                                                         | No IRF                                                                   |                                                                     |                                                                     |                 | *P = 0.045 vs. no IRF at baseline                                                                                                          |
|                              |                                                                         | Baseline: 0.54 ± 0.22                                                    |                                                                     |                                                                     |                 |                                                                                                                                             |
|                              |                                                                         | Month 4: 0.36 ± 0.20                                                     |                                                                     |                                                                     |                 |                                                                                                                                             |
|                              |                                                                         | Month 6: 0.44 ± 0.29                                                    |                                                                     |                                                                     |                 |                                                                                                                                             |
| Chakravarthy et al 2020[^29] | Change in VA (ETDRS letters)                                            | 5 letters gain (no SRF/IRF at ≥2 visits)                                | 3-Letter difference between groups P = 0.042 Sensitivity analysis: No association (P = 0.111) | 3-Letter difference between groups P = 0.006 Sensitivity analysis: Association (P = 0.036) | N/A             | At 12 months: Higher number of monitoring visits associated with absence of fluid correlate with better VA gain Significant association of IRF with VA. |
| Ref                          | Outcome Description                                                                 | No Fluid       | SRF            | IRF            | Both SRF and IRF | Key Points                                                                 |
|------------------------------|-------------------------------------------------------------------------------------|----------------|----------------|----------------|-----------------|-----------------------------------------------------------------------------|
| de Massougnes et al 2018<sup>30</sup> | BCVA change (by presence of foveal SRF; ETDRS letters)                              | 1.8 ± 18.1     | 9.4 ± 11.8     | N/A            | N/A             | At 12 months: Visual improvement associated with VA at BL, foveal SRF, and female gender AFL favored (vs. RAN) for PED reduction |
| Inan et al 2019<sup>25</sup>   | BCVA (logMAR)                                                                        | No SRF         | Baseline: 1.02 ± 0.55 | Baseline: 1.17 ± 0.5 | N/A             | At 12 months: Anatomic improvement and increased VA observed in groups with and without PED, IRC, and SRF Inverse correlation between pretreatment CMT, IRC and posttreatment IRC, and final BCVA |
| Jaffe et al 2016<sup>37</sup> (VIEW 1 and 2) | ETDRS letters LS mean change from baseline                                      | RAN4: 9.5      | N/A            | N/A            | RAN4: 8.5        | At 12 months: Pattern of visual outcomes was similar regardless of fluid type Eyes with persistent early fluid may benefit from AFL4 vs. AFL8 or RAN4 |

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| Ref            | Outcome Detection | No Fluid     | SRF         | IRF         | Both SRF and IRF | Key Points                                                                 |
|----------------|-------------------|--------------|-------------|-------------|-----------------|-----------------------------------------------------------------------------|
| Jaffe et al 2013 \[13\] NCT00593450 (CATT) | Mean ± SE VA (ETDRS letters) | No SRF 68; No IRF 71.2 ± 0.7 | Foveal SRF: 71; Extrafoveal SRF: 70; $P = 0.051$ | Foveal IRF: 62.4 ± 1.3; Extrafoveal IRF: 67.2 ± 1.0 $P < 0.0001$ | N/A At 12 months: Little association between fluid type and VA At all time points residual IRF, especially foveal IRF, correlated with worse VA vs. no IRF |
| Kodjikian et al 2018 \[19\] NCT01170767 | Fluid as predictor of BCVA (letters) on multivariate analysis | N/A | Change in BCVA SRF at BL No: 3.5 ± 1.8; Yes: 3.8 ± 0.9 ($P = 0.90$) | Change in BCVA IRF at BL No: 6.4 ± 1.4; Yes: 0.9 ± 1.2 ($P < 0.01$) | N/A At 12 months: IRF was associated with lower BCVA score, less improvement in BCVA, and poor prognosis |
| Lin et al 2020 \[18\] | Extended remission (absence of hemorrhage, IRF/ SRF, and leakage for 52 weeks after cessation of anti-VEGFs) | N/A | N/A | Extended remission achieved earlier in eyes with isolated IRF at BL HR 2.05; 95% CI 1.929–4.520; $P = 0.045$ vs. eyes with IRF + SRF | N/A At 12 months: Extended remission achieved earlier in eyes with isolated IRF at presentation |
| Ogasawara et al 2018 \[31\] | Association of VA loss and fluid | N/A | Univariate standardized $\beta$: −0.103; $P = 0.501$ Multivariate standardized $\beta$: −0.203; $P = 0.039$ | Univariate standardized $\beta$: 0.195; $P = 0.189$ Multivariate N/A | N/A At 12 months: Highest gains in BCVA were associated with no PED, SRF, and poor BCVA at BL |
| Pokroy et al 2018 \[26\] | Mean ± SD BCVA LogMAR | No SRF BL: 0.87 ± 0.66; Month 12: 0.93 ± 0.67; No IRF BL: 0.43 ± 0.43; Month 12: 0.47 ± 0.45 | BL: 0.61 ± 0.51; Month 12: 0.66 ± 0.59 $P = 0.01$ vs. no SRF | BL: 0.88 ± 0.59; Month 12: 0.95 ± 0.67 $P < 0.001$ vs. no IRF | N/A At 12 months: BL IRF was prognostic for poorer VA Supports use of SHRM as a prognostic biomarker |
| Ref                                    | Outcome | No Fluid | SRF at BL | IRF at BL | Both SRF and IRF | Key Points                                                                 |
|----------------------------------------|---------|----------|-----------|-----------|------------------|-----------------------------------------------------------------------------|
| Regillo et al 2015¹⁷                    | BCVA of ≥20/40 at Month 12 | N/A      | SRF at BL Yes: 56% | IRF at BL | N/A             | At 12 months: Presence of SRF at BL was predictive of improved VA outcomes |
| NCT00891735 (HARBOR)                  |         |          |           |           |                  |                                                                             |
| Ritter et al 2014¹⁸                     | BCVA (ETDRS letters) | N/A      | SRF at BL No significant effect on BCVA ($P = 0.704$) | IRF at BL | Significantly reduced BCVA gain ($P = 0.006$) | At 12 months: IRC had a strong negative predictive value for visual improvement in both groups |
| NCT00433017 (MONT BLANC)              |         |          |           |           |                  |                                                                             |
| Waldstein et al 2016¹²                 | Change in BCVA (ETDRS letters) ± SE vs. no fluid Index | 2.11 ± 0.89 | $P = 0.018$ vs. no SRF | −2.77 ± 0.73 | $P < 0.001$ vs. no IRF | At 12 months: Greater fluid resolution in all compartments with AFL4 vs. ALF8 or RAN4 IRC was associated with lower BL VA and poorer VA outcomes |
| NCT00637377 NCT00509795 (VIEW 1 and 2) |         |          |           |           |                  |                                                                             |
| Waldstein et al 2016⁶                   | Change in BCVA per BL fluid status | No SRF at BL Freq: 11.3 letters Infreq: −1.0 letters | SRF at BL Freq: 6.3 letters | N/A             |                  | At 12 months: BL SRF was predictive of BCVA gains |
| NCT00275821 (EXCITE)                  |         |          |           |           |                  |                                                                             |
| Wickremasinghe et al 2012²²            | BCVA (logMAR) | N/A      | BL: 0.55 12 months: 0.54 ($P = 0.07$ vs. IRF) | BL: 0.79 ($P = 0.006$ vs. SRF alone) 12 months: 0.78 | N/A             | At 12 months: Dry eyes/eyes with SRF had improved BCVA vs. eyes with residual IRF; BL IRF confers significantly worse prognosis for visual outcome |

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| Ref                          | Outcome                  | No Fluid | SRF | IRF                     | Both SRF and IRF | Key Points                                                                 |
|------------------------------|--------------------------|----------|-----|-------------------------|------------------|-----------------------------------------------------------------------------|
| Wickremasinghe et al 2016    | Mean ± SD BCVA (ETDRS letters) | 59.4 ± 12.9 | 61.2 ± 11.9 | 54.6 ± 17.8*<i>P < 0.001</i> vs. no fluid/SRF | N/A              | At 20.8 months (mean): New occurrence of IRF/SRF more likely to lead to BCVA loss vs. dry eyes or persistent IRF/SRF |
| Kim et al 2017               | BCVA (logMAR)            | N/A      |     | IRF with or without SRF |                  | N/A                                                                         |
| Schmidt-Erfurth et al 2020   | Correlation of fluid location and quantification with BCVA | N/A      |     | Volume-dependent negative effect on vision |                  | N/A                                                                         |
| Sharma et al 2016            | Mean ± SE BCVA (ETDRS letters) | No foveal SRF/IRF: 69.7 ± 1.2 (<i>P = 0.049</i> vs. any type of foveal or extrafoveal fluid) | No SRF: 66.6 ± 0.7 Foveal SRF: 72.8 ± 1.5 Extrafoveal SRF: 69.6 ± 1.2 (<i>P = 0.0005</i> foveal SRF vs. extrafoveal SRF or no SRF) | No IRF: 72.2 ± 0.8 Foveal IRF: 59.3 ± 1.5 Extrafoveal IRF: 65.3 ± 0.9 (<i>P < 0.0001</i> for both groups vs. no IRF) | N/A | At 24 months: Foveal IRF, abnormally thin retina, greater thickness of the subretinal tissue complex, and subfoveal geographic atrophy or scar had the worst VA. Foveal SRF had better VA than no SRF |
Table 2.  (Continued)

| Ref                | Outcome                        | No Fluid | SRF                | IRF                | Both SRF and IRF | Key Points |
|--------------------|--------------------------------|----------|--------------------|--------------------|-------------------|------------|
| Ying et al 2014⁹ (CATT) | Sustained VA loss               | N/A      | Sustained VA loss  | Sustained VA loss  | N/A              | At 24 months: Higher proportions of IRF seen in eyes with sustained VA loss |
|                    | Yes: n = 61                     |          | Yes: 19.2%         | Yes: 82.5%         |                   |            |
|                    | No: n = 969                     |          | No: 36.8% (P = 0.006) | No: 51.0% (P < 0.001) |                   |            |
| Shin et al 2013³⁹  | Mean BCVA                       | N/A      | 20/100             | 20/1,000           | N/A              |            |
| Gianniou et al 2015⁴⁰ | Mean VA (letters) change from baseline | N/A      | Refractory SRF     | Refractory IRF     | N/A              | At 12, 24 and 36 months, VA increased with RAN |
|                    | BL: 65.3 (11.9)                 |          | BL: 53.7 (17.2)    |                   |                   | Higher risk of fibrosis, atrophy, or VA loss with refractory cysts vs. refractory SRF |
|                    | 12 months: +10.4 (13.3)         |          | 12 months: +7.0 (13.8) |                   |                   |            |
|                    | 24 months: +8.2 (14.4)          |          | 24 months: +7.5 (17.0) |                   |                   |            |
|                    | 36 months: +8.6 (11.6)          |          | 36 months: +7.4 (17.4) |                   |                   |            |

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| Ref                          | Outcome                                      | No Fluid               | SRF                              | IRF        | Both SRF and IRF | Key Points                                                                                                                                 |
|------------------------------|----------------------------------------------|------------------------|----------------------------------|------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Guymer et al 2019           | Mean change from baseline in BCVA            | “Intensive” not tolerating SRF | 12 months: 4.0 ± 14.4            | “Relaxed” tolerating SRF | N/A              | At 24 months: Relaxed treatment was noninferior to intensive treatment. Patients on relaxed treatment had fewer injections, and significantly more extended/maintained 12-week treatment intervals vs. patients on intensive treatment. |
| NCT01972789                 |                                              | 24 months: 3.0 ± 16.3  | 12 months: 4.3 ± 12.7            | 24 months: 2.6 ± 16.3 | (P = 0.63 vs. intensive) (P = 0.99 vs. intensive) |                                                                                                                                              |
| Jang et al 2015             | Mean VA change                               | N/A                    | Treatment-refractory SRF         | N/A        | N/A              | Across 36 months: RAN retreatment in nAMD with refractory SRF may still allow good and maintained visual improvement.                             |
|                             |                                              |                        | BL: 65.3 letters                |            | N/A              |                                                                                                                                              |
|                             |                                              |                        | 12 months: +10.4 letters        |            | N/A              |                                                                                                                                              |
|                             |                                              |                        | 24 months: +8.2 letters         |            | N/A              |                                                                                                                                              |
|                             |                                              |                        | 36 months: +8.6 letters         |            | N/A              |                                                                                                                                              |
| Jaffe et al 2019 (CATT)     | Mean VA                                      | N/A                    | No SRF: 61 letters              | No IRF: 68 letters | N/A              | At 5 years: 60% of eyes had IRF and 38% of eyes had SRF IRF was significantly associated with worse VA and VA loss from baseline to year 5. |
|                             |                                              |                        | Extrafoveal SRF: 57 letters     | Extrafoveal IRF: 57 letters | (P < 0.001)     |                                                                                                                                              |
|                             |                                              |                        | Foveal SRF: 68 letters          | Foveal IRF: 44 letters  | (P < 0.001)     |                                                                                                                                              |
|                             |                                              |                        | (P = 0.02)                      |            | N/A              |                                                                                                                                              |
extrafoveal IRF at all evaluated time points ($P < 0.0001$). Conversely, foveal involvement of SRF or sub-RPE fluid at 1 year did not significantly affect visual acuity ($P = 0.051$ and $P = 0.40$, respectively). Intraretinal fluid had a greater negative effect on visual acuity than did SRF or sub-RPE fluid at all time points and was independently associated with worse visual acuity over the course of treatment.

In a post hoc analysis of the VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) trials,12 multivariate modeling indicated that IRF at baseline was associated with a smaller improvement in BCVA at Week 52 ($-2.77$ letters; $P < 0.001$ vs. no IRF), as was baseline pigment epithelial detachment (PED; $-1.88$ letters, $P = 0.012$ vs. no PED). SRF at baseline was associated with a larger BCVA change at Week 52 ($+2.11$ letters; $P = 0.018$ vs. no SRF).

In a retrospective exploratory analysis of the HARBOR trial,17 SRF at baseline was associated with a 2-fold greater likelihood of achieving a Snellen equivalent of 20/40 or better at 1 year than if SRF was absent (multivariate analysis, odds ratio: 2.0; 95% confidence interval 1.2–3.3). Patients with SRF and small lesions ($\leq 4.51$ disk area of total choroidal neovascularization leakage) were more likely to gain $\geq 15$ letters than those with SRF and large lesions (odds ratio: 2.5; 95% confidence interval 1.5–4.3). In a post hoc analysis,8 baseline horizontal IRF extension in the fovea, and IRF volume, had the highest predictive power for concomitant BCVA. Baseline SRF and PED parameters did not contribute to baseline BCVA, regardless of macular location.

In the MONT BLANC trial,18 baseline IRF was associated with a significantly reduced BCVA gain ($P = 0.006$) at 1 year in patients treated with as-needed ranibizumab (monotherapy or with photodynamic therapy), as analyzed by generalized estimation equations. Baseline SRF did not impact BCVA ($P = 0.704$). In a complementary analysis of the GEFAL trial,19 stepwise multivariate analysis identified an association between baseline IRF and a smaller BCVA change at 1 year compared with absence of IRF ($+0.89$ vs. $+6.35$ letters; $P < 0.01$). Baseline SRF did not impact BCVA ($P = 0.98$).

Data on the association between sub-RPE fluid and BCVA were scarce and evaluated only in CATT13 and VIEW.12

Functional Outcomes at Other Time Points

**Randomized studies: Year 2.** Post hoc analyses of the CATT trial14 found that, at Week 104, eyes with foveal SRF had better visual acuity than those without
SRF \((P = 0.0005)\) and eyes with foveal IRF had worse visual acuity than those without IRF \((P < 0.0001)\). The negative effect of IRF on visual acuity was evident at all time points and worsened over time. Furthermore, eyes with sustained visual acuity loss at 2 years were more likely to have IRF \((P < 0.001)\) and thinner SRF \((P = 0.04)\), but less likely to have SRF \((P = 0.006)\). Visual acuity was better in eyes with foveal sub-RPE fluid at Week 104 than eyes with extrafoveal or no sub-RPE fluid \((P = 0.048)\). Sub-RPE fluid at Week 104 was not associated with sustained visual acuity loss at 2 years \((P = 0.13)\).

In the prospective FLUID trial,11 patients received ranibizumab in an intensive (complete resolution of SRF and IRF) or relaxed (complete resolution of IRF and tolerance of \(\leq 200 \mu m\) of SRF in height) treat-and-extend regimen. Two-year results showed no negative effect on vision when SRF up to 200 \(\mu m\) was tolerated, and treatment burden was reduced (15.8 vs. 17.0 injections at Year 2 in the relaxed and intensive groups, respectively).

In a post hoc analysis of the HARBOR trial,20 multivariable mixed-effects modeling showed that a 100 nL increase in IRF negatively affected visual acuity \((-4.00 \text{ letters}; \ P < 0.0001)\), but SRF was associated with good visual acuity outcomes \((+1.10 \text{ letters}; \ P = 0.0046)\). Pigment epithelial detachment did not affect visual acuity \((-0.35 \text{ letters}; \ P = 0.0021)\).

Randomized Studies: Year 5. Similar to the 1- and 2-year analyses of CATT, the presence and foveal involvement of IRF at Year 5 was independently associated with worse visual acuity, with the strength of this association greater by Year 5. Eyes with foveal SRF had better visual acuity than eyes without foveal SRF on univariate analysis, but the relationship was not significant on multivariate analysis \((P = 0.14)\).10 A trend towards better visual acuity was found in eyes with foveal sub-RPE fluid at Year 5 compared with eyes without sub-RPE fluid \((P = 0.006)\) or with extrafoveal sub-RPE fluid \((P = 0.01)\). The absence of baseline SRF was a significant predictor of worse visual acuity at 5 years \((P = 0.03)\).21

Real-World Studies

The association between fluid and visual acuity outcomes has also been assessed in observational studies. Of the 16 real-world studies identified in this systematic review (details in Table 2), statistical data comparing visual outcomes between patients without fluid to those with SRF and/or IRF were available for 11 studies. Owing to variability in study methodology, patient populations, and data analyses, any conclusions should be interpreted with caution.

Only two observational studies were prospective.22,23 In one study22 of patients treated with ranibizumab treat-and-extend, baseline BCVA was significantly worse in eyes with IRF than eyes with SRF alone \((P = 0.006)\). After three injections, eyes that were dry (no IRF/SRF) had better BCVA at Year 1 compared with residual IRF \((P = 0.05)\), whereas eyes with SRF alone had similar BCVA compared with those that were dry. Furthermore, eyes with residual IRF had a greater chance of BCVA loss at Year 1 compared with eyes that were dry \((P = 0.01)\). In a retrospective analysis of another prospective study of patients treated with ranibizumab treat-and-extend,23 eyes with IRF had significantly lower BCVA at any time point than eyes that were dry or those with SRF \((P < 0.001)\).

Five retrospective, observational studies found that eyes with baseline IRF had worse vision at Month 4,24 Year 1,25–27 or Year 228 than eyes without as determined by multivariate analysis. In addition, eyes with \(\geq 2\) clinic visits without IRF had significantly greater gains in visual acuity compared with eyes with fewer IRF-free visits.29 Three retrospective, observational studies found that eyes with baseline SRF had better vision at Year 120,31 or Year 228 than eyes without. In one study, baseline foveal SRF was a significant predictor of positive change in BCVA at Year 1 \((+10.6 \text{ letters greater than eyes without SRF}; \ P = 0.001)\).30 However, four studies found that baseline SRF did not significantly affect visual acuity at Months 4 and 6,24 or Year 1.25–27 Another study found that visual acuity in eyes with \(\geq 2\) clinic visits without SRF was not significantly different from those with fewer SRF-free visits.29 In addition, in eyes with SRF and PED, BCVA was not significantly different between patients with persistent SRF and those without SRF or IRF at any visit.32

Number of Injections

Association between fluid compartments and anti-VEGF injection frequency was assessed as a marker for treatment burden. Of the studies identified (Table 3), only the FLUID study found significant associations between fluid presence/absence and number of injections.11 The mean number of injections was lower in the relaxed (tolerating \(\leq 200 \mu m\) of SRF) group than in the intensive (not tolerating SRF) group at Year 1 \((8.9 \pm 2.3 \text{ vs. } 9.5 \pm 2.6; \ P = 0.001)\) and Year 2 \((15.8 \pm 5.9 \text{ vs. } 17.0 \pm 6.5; \ P = 0.001)\).

Discussion

This review provides a comprehensive, objective, and systematic critique of the relationship between
Table 3. Association Between Fluid and Number of Injections

| Ref             | Study Design | Risk of Bias | Treatment | Protocol | Previous Treatments | Treatment Arm | N  | No. of Injections | Time Point |
|-----------------|--------------|--------------|-----------|----------|---------------------|---------------|----|-------------------|------------|
| Curry et al 2017 | Open-label   | Mod          | AFL       | PRN      | RAN                 | Eyes with IRF | 9  | Injection frequency 46 days ($P = 0.02$) | 12 months |
|                 |              |              |           |          |                     | Eyes with SRF | 11 | Injection frequency 41 days ($P = 0.10$) |            |
| Dervenis et al 2016 | Observational | Low          | RAN       | PRN      | Treatment-naive    | SRF           | 42 | 3.9               | 12 months |
|                 |              |              |           |          |                     | No SRF        | 20 | 3.3               |            |
|                 |              |              |           |          |                     | IRF           | 32 | 3.7               |            |
|                 |              |              |           |          |                     | No IRF        | 30 | 3.9               |            |
| Ersoy et al 2014 | Observational | Low          | RAN or BEV| PRN      | Mixed              | Persistent SRF | 14 | 7.1 (2.6)         | 12 months |
|                 |              |              |           |          |                     | No persistent SRF | 16 | 5.4 (1.8)         |            |
| Guymer et al 2019 | RCT          | Low          | RAN       | T&E      | Treatment-naive    | “Intensive” not tolerating SRF or IRF | 349 | 9.5 (2.6)         | 12 months |
|                 |              |              |           |          |                     | “Relaxed” tolerating SRF $\leq 200 \mu m$ | 8.9 (2.3)* |        | 24 months |
| Regillo et al 2015 | RCT post hoc | Low          | RAN       | PRN      | Treatment-naive    | SRF thickness $>118.25 \mu m$ | 117 | 8.9               | 12 months |
|                 |              |              |           |          |                     | SRF thickness $\leq 118.25 \mu m$ | 134 | 7.3               |            |
| Ritter et al 2014 | RCT          | Low          | RAN or RAN + PDT | PRN | Treatment-naive | With SRF | 82 | RAN+PDT: 5.3 (2.2) | 12 months |
|                 |              |              |           |          |                     | Without SRF  | 75 | RAN: 5.6 (2.4)    |            |
|                 |              |              |           |          |                     | With IRF     | 40 | RAN+PDT: 4.4 (2.3)* |            |
|                 |              |              |           |          |                     | Without IRF  | 55 | RAN: 4.8 (1.8)    |            |
|                 |              |              |           |          |                     |               | 60 | *$P < 0.01$ vs. with SRF |            |
|                 |              |              |           |          |                     |               | 69 | RAN + PDT: 5.0 (2.3) |            |
|                 |              |              |           |          |                     |               | 62 | RAN: 5.2 (2.0)    |            |
|                 |              |              |           |          |                     |               | 61 | RAN + PDT: 4.9 (2.2) |            |

AFL, aflibercept; BEV, bevacizumab; BL, baseline; IRF, intraretinal fluid; Mod, moderate; PDT, photodynamic therapy; PRN, pro re nata; RAN, ranibizumab; RCT, randomized controlled trial; T&E, treat-and-extend.
fluid compartments and visual acuity in patients with nAMD treated with anti-VEGF drugs. This is the first systematic review objectively approaching this topic based on published evidence in the peer-reviewed literature. The conclusions presented are primarily drawn from prespecified and post hoc analyses of randomized controlled trials in patients with nAMD and are corroborated by real-world evidence.

The findings suggest that baseline and persistent/new IRF negatively affect visual acuity throughout treatment and the strength of this association increases from Years 1 and 2 to Year 5. Location of IRF relative to the foveal center influences vision outcomes—foveal IRF is generally associated with worse visual acuity compared with extrafoveal IRF or absence of IRF. A post hoc analysis of the HARBOR study suggested that IRF has a volume-dependent negative impact on vision but volumetric assessments are not commonplace in clinical practice and are not currently part of retreatment criteria.

Data regarding the role of SRF are unclear. Most studies suggested that SRF did not negatively affect visual acuity at baseline or throughout Year 1 of treatment. At Year 2, one study corroborated the Year 1 findings and another found that SRF was associated with improved vision outcomes. In the study exploring long-term effects of SRF on visual acuity, patients with foveal SRF at any time point had better vision at Year 5 than those without SRF.

Few studies reported visual acuity outcomes stratified by the presence/absence of sub-RPE fluid. Some reported that there was no vision loss when sub-RPE fluid was present, but visual acuity benefits could not be ascertained. One study reported that foveal sub-RPE fluid was associated with better visual acuity at Year 5, but the explanation for this effect is unclear. In some instances, sub-RPE fluid may reflect Type 1 choroidal neovascularization, providing trophic support to the retina.

Likewise, few studies associated the number of injections with fluid status, and because a difference between the number of injections according to IRF and SRF status was not apparent, it was not possible to draw any clinically meaningful conclusions.

There are several possible explanations why IRF but not SRF is associated with worse visual acuity. IRF may indicate Müller cell dysfunction, which adversely affects photoreceptor function and neural transmission through the retina. Disruption of the blood–retinal barrier promotes capillary albumin escape and fluid accumulation in the interstitial space. Intraretinal fluid may indicate a damaged external limiting membrane. It has been hypothesized that hyperreflective cystoid structures seen on optical coherence tomography may represent tissue loss mediated by non–VEGF-driven mechanisms, such as cell death, and evidence suggests that some neurosensitive damage is not reversible by treatment. Conversely, SRF may indicate an intact, functioning photoreceptor/external limiting membrane. Decrease in SRF, which acts as a spatial buffer between photoreceptors and toxic metabolites, may result in misalignment and decay of photoreceptors, thereby affecting ellipsoid zone integrity.

Furthermore, Type 1 macular neovascularization might be a compensatory response to localized ischemia, and the source of the SRF bathes the photoreceptors with nutrients, oxygen, and neuroprotective substances that may improve photoreceptor function and lead to better visual acuity.

Although the studies in this systematic review had a low/moderate bias risk, many were retrospective or evaluated fluid post hoc and were not formally powered to test our hypothesis. Different methodologies reported various outcomes, time points, and definitions of SRF/IRF, making a robust meta-analysis unfeasible. Different statistical methods (univariate or multivariate analysis) were applied for evaluating the association between IRF, SRF, and sub-RPE fluid with visual acuity, which may explain some differences in the findings across the various studies. In addition, we did not include data presented at international conferences that should be considered once validated in peer-reviewed publications.

Clinical insights are usually derived from robust evidence from prospective trials, but only the FLUID trial prospectively correlated fluid location with visual acuity, demonstrating a need for additional randomized controlled trials to characterize the effects of fluid compartments on visual acuity. Comparisons of real-world evidence with randomized controlled trials data should be interpreted with caution; most real-world evidence was retrospective and varied in methodology. More observational studies are needed to support additional evidence generation.

A low correlation exists between overall changes in morphology and visual acuity in patients treated with anti-VEGF drugs, but our systematic review shows that the presence of IRF is associated with poorer visual acuity. Subretinal fluid does not negatively affect VA at Year 1, and data after Year 1 suggest that the presence of SRF is associated with better visual acuity than if absent.

To optimally manage patients with nAMD with anti-VEGF drugs, clinicians should understand the impact of fluid compartment changes on visual acuity. Current evidence suggests that after an initial treatment course, anti-VEGF regimens that do not tolerate IRF but tolerate stable persistent SRF (on the condition that...
visual acuity is stable/improved) may enable patients to achieve their best visual acuity and minimize treatment burden. In addition to the fluid compartment, the location of the fluid relative to the foveal center should be considered when making retreatment decisions. Additional confirmatory studies are warranted to validate the differential effects of fluid compartments on functional outcomes (http://links.lww.com/IAE/B512).

Key words: antivascular endothelial growth factor treatment, neovascular age-related macular degeneration, retinal fluid compartments, subretinal fluid, intraretinal fluid, systematic literature review.

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