Anti-VEGF–Resistant Subretinal Fluid Is Associated With Reduced Risk of Macular Atrophy and Better Visual Acuity: Drug-Induced Choroidal New Vessel Homeostasis?

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Disclosures

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Background and Objective

• Clinical trial experience suggests that the best vision outcomes in nAMD are observed when the steady state induced by anti-VEGF treatment includes some residual (i.e., treatment-resistant) SRF\textsuperscript{1-3}

• Using HARBOR data, we investigated the effect of SRF thickness on vision outcomes (BCVA, MA) using a 50-µm scale:
  • 0 µm
  • > 0–50 µm
  • > 50–100 µm
  • > 100 µm

• In HARBOR, all eyes were treated aggressively and SRF persisted despite aggressive therapy.

The HARBOR Trial (NCT00891735) Compared Monthly and PRN Ranibizumab in nAMD for 24 Months

Treatment-naïve patients with nAMD and active subfoveal CNV (N = 1097)

- 0.5 mg Monthly (n = 275)
- 0.5 mg 3 LD + PRN (n = 275)
- 2.0 mg Monthly (n = 274)
- 2.0 mg 3 LD + PRN (n = 273)

Re-treatment criteria for the PRN groups:
≥ 5-letter decrease in BCVA from previous visit or any evidence of disease activity on SD-OCT (SRF, IRF, or subretinal pigment epiretinal fluid)

BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; IRF, intraretinal fluid; LD, loading dose; nAMD, neovascular age-related macular degeneration; PRN, as-needed; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid.
Study Design

• Post hoc analysis of HARBOR (NCT00891735)
• All treatment arms pooled, and analysis limited to eyes with SRF at screening, baseline, or week 1 (n = 785)

• Outcomes:
  • **SRF** presence and thickness evaluated using SD-OCT imaging
    • Eyes grouped according to SRF thickness:
      • 0 µm, > 0–50 µm, > 50–100 µm, or > 100 µm
  • **BCVA** assessed using standard ETDRS protocols
  • **MA** presence determined from fluorescein angiograms and color fundus photographs by masked graders

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; MA, macular atrophy; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid.
### Subretinal Fluid

- **Definition:** exudation occurring between the photoreceptor layer and the RPE
- **Determined from all B-scans for each patient**
- **All evaluations assessed by 2 masked graders**
- **A third grader adjudicated any discrepancies between the first 2 assessments**

### Macular Atrophy

1. **Definition:** sharply demarcated areas of RPE depigmentation with increased visibility of choroidal vessels through the lesion on CFP or FA, ≥ 250-μm diameter, corresponding to flat areas of well-demarcated staining on FA
- **Included all atrophy immediately within, adjacent to, and nonadjacent to CNV lesions (active or regressed)**

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CFP, color fundus photograph; CNV, choroidal neovascularization; FA, fluorescein angiography; RPE, retinal pigment epithelium.
Ranibizumab-Treated Eyes With Residual SRF Had Greater Mean BCVA Than Eyes With No SRF Regardless of SRF Thickness

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, subretinal fluid.
Mean Change in BCVA Was Similar Between Eyes With or Without Residual SRF

Mean Change in BCVA at Month 12 by SRF Status at Month 12

Mean Change in BCVA at Month 24 by SRF Status at Month 24

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, subretinal fluid.
In Eyes With No MA at Baseline, Residual SRF Was Associated With Reduced Risk of Developing MA

MA, macular atrophy; SRF, subretinal fluid.

P < 0.0001

P < 0.0001

P < 0.0001
AMD-related changes in the retina/choroid interface

- Impaired oxygen transport
  - Hypoxia
    - ↑ VEGF-A expression
      - Choroidal neovascularization
        - SRF

The SRF could potentially be a manifestation of an imperfect yet critical “survival mechanism” for the degenerating macula


AMD, age-related macular degeneration; SRF, subretinal fluid; VEGF-A, vascular endothelial growth factor-A.
AMD-related changes in the retina/choroid interface

- Impaired oxygen transport
- Hypoxia
- Atrophy

VEGF-A

Choroidal neovascularization

SRF

The cessation or absence of this imperfect “survival mechanism” may be a harbinger of the development of atrophic changes

AMD, age-related macular degeneration; SRF, subretinal fluid; VEGF-A, vascular endothelial growth factor-A.
Conclusions

• We analyzed SRF in 50-µm increments and found no threshold detrimental to vision outcomes over 2 years

• Rates of MA were significantly higher in the absence of SRF

• These findings are consistent with earlier analyses\(^1\)\(^-\)\(^3\)

• Persistent SRF in the course of anti-VEGF treatment may be a sign of persistent choroidal new vessel perfusion with transudation, which may operate as an imperfect compensatory mechanism that maintains the function of the degenerating macula\(^1\)\(^-\)\(^15\)


MA, macular atrophy; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.