Is Residual Subretinal Fluid (SRF) Associated With Improved Vision Outcomes? Evaluation of Fluorescein Angiography (FA) Patterns From the HARBOR trial

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Disclosures

• Financial disclosures
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• Study disclosures
  − This study includes research conducted on human subjects
  − Institutional Review Board approval was obtained prior to study initiation
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Summary

- This *post hoc* analysis of data from HARBOR\(^1\) (NCT00891735) evaluated the potential relationship of SRF thickness with VA over 2 years of monthly or PRN ranibizumab 0.5 mg or 2 mg treatment in patients with nAMD stratified by good (20/40 or better) or bad vision (worse than 20/40)
- In univariate analyses, numerous staining, fibrosis, and atrophy variables differed between patients with good or bad vision
- In multivariable analyses, characteristics predictive of the odds of good vision included:
  - At month 12
    - Absence of Subfoveal fibrosis with PRN ranibizumab
  - At month 24
    - Presence of a window defect
    - Absence of Subfoveal atrophy
- SRF was associated with lower rates of MA (all patients) and fibrosis (bad vision only), but higher rates of PED (all patients)

*mean±SE
MA, macular atrophy; nAMD, neovascular age-related macular degeneration; PRN, *pro re nata* (as needed); SRF, subretinal field; VA, visual acuity; VEGF, vascular endothelial growth factor
Background and Objective

• In CATT, after 2 years of monthly or PRN anti-VEGF therapy including ranibizumab for AMD, patients with foveal SRF demonstrated significantly better VA that those with extrafoveal SRF or without SRF ($P = 0.0005$)
  
  - Foveal SRF – $72.8 \pm 1.5^*$ letters
  - Extrafoveal SRF – $69.6 \pm 1.2^*$ letters
  - Without SRF – $66.6 \pm 0.7^*$ letters

• **Objective:** To evaluate the relationship between SRF thickness at screening or week 1 with vision outcomes in patients with nAMD treated with intravitreal injections of ranibizumab

*mean±SE
AMD, age-related macular degeneration; CATT, Comparison of Age-related Macular Degeneration Treatments Trials; nAMD, neovascular age-related macular degeneration; PRN, *pro re nata* (as needed); SRF, subretinal fluid; VA, visual acuity; VEGF, vascular endothelial growth factor
Treatment-naïve patients (aged ≥50 years) with nAMD, active subfoveal CNV, and BCVA 20/40 to 20/320 (Snellen equivalent) using ETDRS (N = 1097)

0.5 mg Monthly (n = 275)

0.5 mg PRN (with 3-mo LD) (n = 275)

2.0 mg Monthly (n = 274)

2.0 mg PRN (with 3-mo LD) (n = 273)

*PRN re-treatment criteria:
- ≥5-letter decrease in BCVA from previous visit
- Any evidence of disease activity on SD-OCT

HARBOR Study Design

A large, prospective phase 3 trial (NCT00891735) that evaluated efficacy of 2 doses and 2 regimens of ranibizumab for nAMD over 2 years


BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; LD, monthly loading doses; mo, month; nAMD, neovascular age-related macular degeneration; PRN, pro re nata (as needed); SD-OCT, spectral-domain optical coherence tomography.
Endpoints and Sub-analyses

• Patients
  - HARBOR patients who had presence of SRF evaluated by OCT at screening, baseline or week 1 as well as months 12 and/or 24
  - Stratified by good (20/40 or better) and bad vision (worse than 20/40) at M12 and M24
  - Treatment arms pooled

• Endpoints and Analyses
  - Univariate analyses of staining, fibrosis, and atrophy characteristics at months 12 and 24 by good vs bad vision
  - Multivariable analyses of factors predictive of good vision at months 12 and 24
  - Rates of MA, fibrosis, and PED by fluid status evaluated at months 12 and 24
  - CNV area and leakage area at baseline and change from baseline by good vision vs bad vision at months 12 and 24

FA, fluorescein angiography; MA, macular atrophy; PED, pigment epithelial detachment
Statistically Significant Univariate Associations at Baseline and Months 12 or 24
Good (20/40 or Better) vs Bad Vision (Worse Than 20/40)

*All *P* < 0.05 in univariate analyses comparing proportion of patients with good vision vs bad vision.

CI, confidence interval; M12, month 12; M24, month 24; PRN, *pro re nata* (as needed), VA, visual acuity.
Multivariable Regression: Factors Associated With Vision at Months 12 or 24

CI, confidence interval; M12, month 12; M24, month 24; PRN, pro re nata (as needed); VA, visual acuity.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
<th>Month 12</th>
<th>Month 24</th>
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</thead>
<tbody>
<tr>
<td>Fibrosis Subfoveal (Monthly Arms)</td>
<td>0.77 (0.24, 2.40)</td>
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<td></td>
</tr>
<tr>
<td>Fibrosis Subfoveal (PRN Arms)</td>
<td>0.37 (0.16, 0.81)</td>
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<td></td>
</tr>
<tr>
<td>Atrophy Subfoveal</td>
<td>0.15 (0.04, 0.65)</td>
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<tr>
<td>Window Defect</td>
<td>3.04 (1.39, 6.67)</td>
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</tbody>
</table>
With Good (20/40 or Better) and Bad (Worse Than 20/40) Vision, MA and PED Were Significantly Associated With Fluid Status at Month 12

- SRF was associated with less atrophy and more PED than IRF or no fluid
- In patients with bad vision, fibrous tissue was higher with IRF than SRF
With Good (20/40 or Better) and Bad (Worse Than 20/40) Vision, MA and PED Were Significantly Associated With Fluid Status at Month 24

- A lower proportion of SRF (vs IRF or no fluid) patients had atrophy and more had PED
- In patients with bad vision, fibrous tissue was more common with IRF than SRF

*P-values assess for any difference in each structural change across fluid groups; no pairwise comparisons were conducted to analyze differences between individual fluid subgroups

1MA includes patients with CD (Good Vision: no fluid 3.8%, IRF only 6.9%, SRF only 2.6%, SRF and IRF 4.5%. Bad Vision: no fluid 4.2%, IRF only 3.1%, SRF only 6.5%)
Trend for Eyes with Bad Vision (vs Good Vision) to Have a Larger Change From Baseline in CNV at Month 12

- No clinically significant differences between patients with good vision (20/40 or better) or bad vision (worse than 20/40) in change from baseline values of:
  - Total area of CNV (DA) at months 12 or 24
  - Total area of leak CNV at months 12 or 24

- In patients who had residual SRF, total area of CNV (DA) and CNV leakage were higher at baseline in eyes with bad vs good vision

- There was a trend for larger reductions in total area of CNV (DA) and CNV leakage in eyes with bad vs good vision at month 12

CNV, choroidal neovascular membranes; DA, disc area
Conclusions

• In univariate analyses of data from HARBOR, rates of staining, fibrosis, and atrophy differed between patients with good (20/40 or better) vs bad (worse than 20/40) vision in eyes with residual SRF.

• In multivariable analyses, factors predictive of good vision in eyes with residual SRF at months 12 or 24 included:
  − Absence of subfoveal fibrosis at month 12 in the PRN arms
  − Absence of subfoveal atrophy at month 24
  − Presence of window defect at month 24

• Presence of residual SRF at months 12 and 24 was associated with:
  − Lower rates of MA
  − Higher rates of PED
  − Lower rates of fibrosis (in eyes with bad vision only)

MA, macular atrophy; PED, pigment epithelial detachment; SRF, subretinal field.