Impact of Retinal Neurodegenerative Changes in Patients with Diabetic Macular Edema from the VISTA Study

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BACKGROUND & PURPOSE

- Retinal thickness measured by optical coherence tomography (OCT) has limited predictive value for visual acuity in patients with diabetic retinopathy (DR) and diabetic macular edema (DME)[1,2]
- The disorganization of retinal inner layers (DRIL) represents a potential structural biomarker for loss of visual function in DR, and has been associated with worse visual acuity, increased retinal nonperfusion (RNP), disease severity, and risk of proliferative diabetic retinopathy (PDR)[3-5]
- Presence of DRIL is also associated with loss of integrity in the external limiting membrane (ELM) and ellipsoid zone (EZ), which has been shown to correlate with loss of visual acuity[3,6]
- This study evaluated the impact of retinal neurodegenerative changes in patients with DME from the VISTA study

METHODS

- VISTA was a randomized, multicenter, double-masked trial that randomized 466 patients with DME to IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks (2q8) after 5 initial monthly doses, or laser control
- Extent of DRIL, ELM loss, and EZ loss were quantified as microns in the central 1000-μm macular area based on OCT images at baseline and Weeks 52 and 100 by Duke Reading Center
- Changes in markers of retinal neurodegeneration and their correlation with visual and anatomical parameters were evaluated at Weeks 52 and 100
- RNP was assessed on fluorescein angiography; Diabetic Retinopathy Severity Scale (DRSS) score was assessed on fundus photography
- Only gradable images were used in this analysis
- Statistical analyses included Pearson correlation and analysis of covariance (ANCOVA); P-values <0.05 were considered nominally significant; observed case values were used in the analysis

CONCLUSIONS

- At Weeks 52 and 100, in patients with DME, those treated with IAI had greater improvement in DRIL and better preservation of EZ and ELM compared with laser
  - Across all treatment groups, DRIL, ELM loss, and EZ loss had a moderate negative correlation with BCVA, and weak correlations with DRSS score and RNP area
  - There was a trend towards less DRIL, EZ loss, and ELM loss in eyes with better baseline visual acuity
- In eyes treated with IAI, greater DRIL improvement at Week 100 was observed in eyes with larger baseline DRIL (>240 μm). However, anatomy preservation at Week 100 was greater in eyes with lower baseline DRIL (≤120 μm)
  - Similarly, ELM and EZ were only partially restored in eyes with ELM and EZ loss at baseline, despite treatment with IAI
- These data support the importance of early treatment with IAI for anatomy preservation, which may help to achieve better visual outcomes

REFERENCES

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3. Nair A and Modi V. Retinal Physician. 2020;17:16–19.
4. Sun JK et al. JAMA Ophthalmol. 2014;132:1309–1316.
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RESULTS

### Changes in Markers of Retinal Neurodegeneration Over Time

- DRIL extent continued to improve from baseline through Week 100 with intravitreal aflibercept injection (IAI) treatment (Figure 1A)
- Extents of ELM and EZ loss were stabilized with continued IAI treatment compared to its progression with laser through Week 100 (Figure 1B and C)
- Among gradable eyes, DRIL more often improved in eyes treated with IAI than with laser, EZ loss was improved or stabilized, and ELM loss was stabilized in more eyes treated with IAI than laser through Week 100

Figure 1. Changes in Markers of Retinal Neurodegeneration Through Week 100
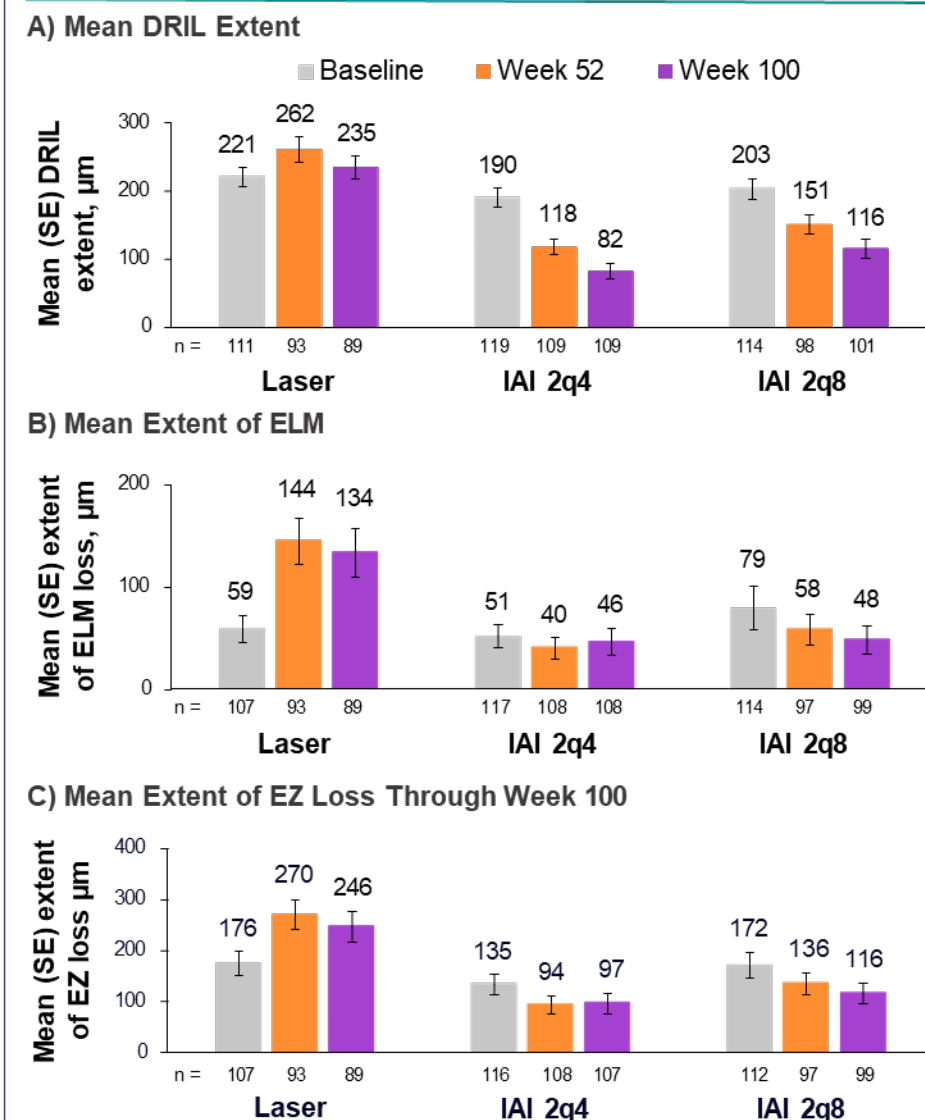
FAS, OC. The number of patients with missing data with laser, IAI 2q4, and IAI 2q8 at baseline was 47, 38, and 39, respectively, at Week 52 was 61, 46, and 54, respectively, and at Week 100 was 65, 47, and 52, respectively.

Correlation Between Markers of Retinal Neurodegeneration and Visual and Anatomic Parameters

- At baseline, there was a moderate positive correlation between ELM and EZ loss and a moderate negative correlation between these 2 parameters and best-corrected visual acuity (BCVA) (Figure 2A)
- At Weeks 52 and 100, DRIL, ELM loss, and EZ loss had a moderate negative correlation with BCVA, and overall weak correlations with DRSS score and RNP area (Figure 2B)
  - Regardless of treatment group, at Week 100, there was a moderate to strong positive correlation between DRIL, ELM loss, and EZ loss (r range: 0.49 to 0.94)

Figure 2. Correlations between Markers of Retinal Neurodegeneration and BCVA, DRSS score and RNP

A) Baseline

Strength of correlation: Weak (r ≤0.39) | Moderate (r = 0.4–0.69) | Strong (r >0.7)

	DRIL	ELM Loss	EZ Loss
DRIL	1		
ELM Loss	0.32 (n=335)	1	
EZ Loss	0.35 (n=332)	0.66 (n=334)	1
BCVA	−0.17 (n=344)	−0.40 (n=338)	−0.44 (n=335)
DRSS	−0.004 (n=343)	0.06 (n=337)	0.04 (n=334)
RNP	−0.005 (n=159)	0.11 (n=157)	0.22 (n=155)

B) Through Week 100 by Treatment Arm

FAS, OC. Correlation between extent of DRIL, ELM loss, and EZ loss and BCVA, DRSS, and RNP, were determined, adjusted for CST at baseline. n = number of patients with non-missing data from variables being tested in the correlation. CST, central subfield thickness.

Changes in Retinal Neurodegeneration Markers by Baseline BCVA ≥20/40 Versus ≤20/50

- At Weeks 52 and 100, there was a trend towards less DRIL, EZ loss, and ELM loss in eyes with BCVA ≥20/40 versus ≤20/50 (Figure 3)

Figure 3. Magnitude of Difference in Retinal Neurodegeneration in Eyes with Baseline BCVA ≥20/40 Versus ≤20/50
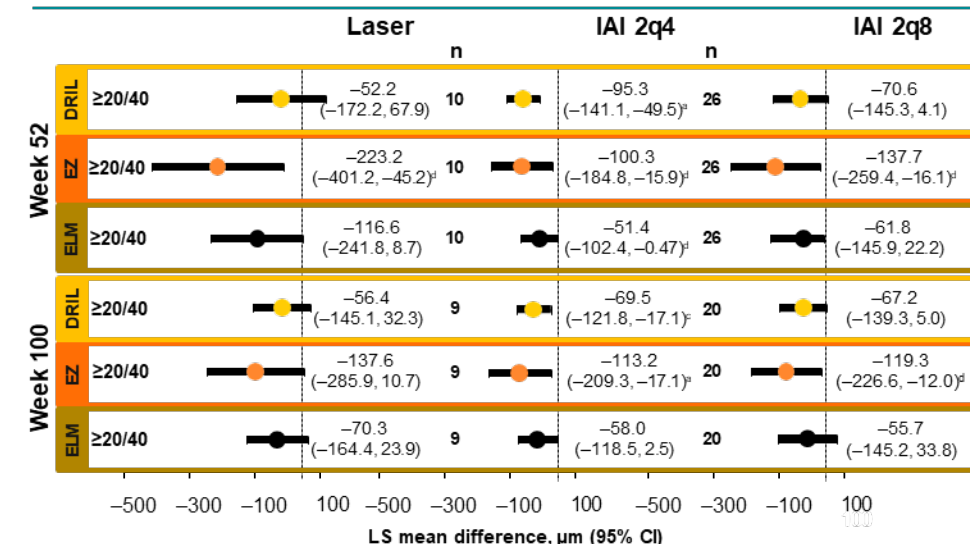

FAS, OC. LS mean difference was determined using an ANCOVA model with CST at Weeks 52 and 100 as covariates. N = number of patients with non-missing DRIL, ELM, or EZ loss, non-missing baseline BCVA, and non-missing CST at Weeks 52 and 100. [a]P≤0.0001; [b]P<0.001; [c]P<0.01; [d]P<0.05 vs reference (BCVA ≤20/50 group). CI, confidence interval; LS, least squares.

### DRIL, ELM Loss, and EZ Loss by Their Respective Baseline Extent

- In eyes treated with IAI, magnitude of improvement in DRIL extent was greater in eyes in tertile (T) 3. However, eyes in T1 treated with IAI had greater preservation of anatomy at Week 100 (Figure 4)
- At Week 100, only partial ELM reconstitution was achieved in eyes with ELM loss at baseline, despite treatment with IAI. Eyes without ELM loss at baseline maintained ELM integrity with IAI treatment (Figure 5)
- Results were similar for EZ loss (Figure 6)

Figure 4. Mean DRIL Extent Through Week 100 by Baseline DRIL Tertile
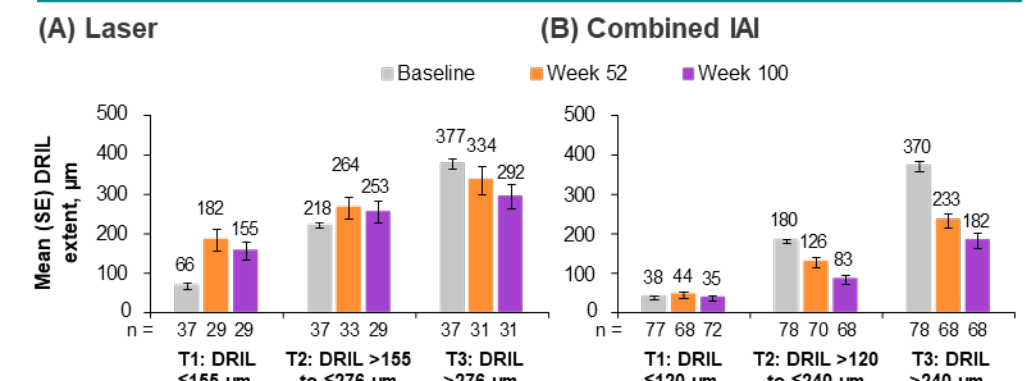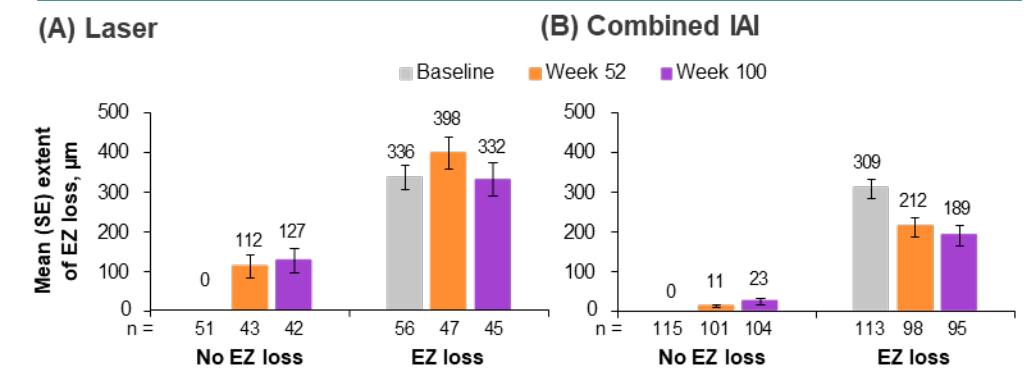

FAS, OC. No missing values at baseline with laser or combined IAI. The number of patients with missing values with laser at Week 52 for T1 was 8, for T2 was 4, for T3 was 6, and at Week 100 for T1 was 8, for T2 was 8, for T3 was 6; missing values with combined IAI at Week 52 for T1 was 9, for T2 was 8, for T3 was 10, and at Week 100 for T1 was 5, for T2 was 10, for T3 was 10.

Figure 5. Extent of ELM Loss Through Week 100 by Baseline ELM Loss Subgroup
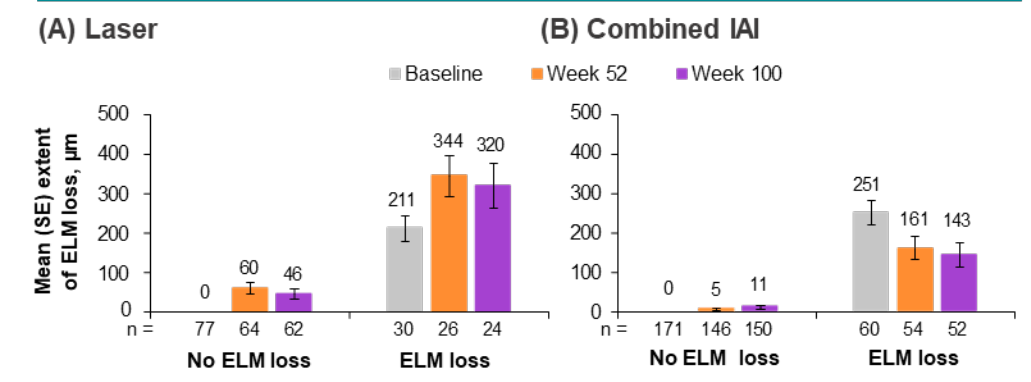
FAS, OC. No missing values at baseline with laser or combined IAI. The number of patients with missing values with laser at Week 52 for no ELM loss was 13, for ELM loss was 4, and at Week 100 for no ELM loss was 15, for ELM loss was 6; missing values with combined IAI at Week 52 for no ELM loss was 25, for ELM loss was 6, and at Week 100 for no ELM loss was 21, for ELM loss was 8.

Figure 6. Extent of EZ Loss Through Week 100 by Baseline EZ Loss Subgroup

FAS, OC. No missing values at baseline with laser or combined IAI. The number of patients with missing values with laser at Week 52 for no EZ loss was 8, for EZ loss was 9, and at Week 100 for no EZ loss was 9, for EZ loss was 11; missing values with combined IAI at Week 52 for no EZ loss was 14, for EZ loss was 15, and at Week 100 for no EZ loss was 11, for EZ loss was 18.