What Happens to Diabetic Retinopathy Severity Scores With Less Aggressive Treatment?

A Post Hoc Analysis of the RISE/RIDE Open-Label Extension Study Examining Instability of DRSS with Intermittent VEGF Suppression

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• Study Disclosures
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Summary

• Post-hoc analysis of changes in DRSS scores in patients from the 12-month RISE and RIDE open-label extension (OLE) who received 0.5 mg ranibizumab PRN

• Patients whose DRSS level improved to ≤ 43 (mild or moderate NPDR) with regular treatment were more prone to worsening when treated intermittently than those who had native DRSS level ≤ 43

• More severe diabetic retinopathy at baseline may indicate more unstable DRSS changes with intermittent dosing
  • This was most pronounced in patients who progressed to PDR – they were the cohort most likely to have the largest swings in DRSS

RISE: NCT00473330; RIDE: NCT00473382.
DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRN, pro re nata.
VEGF Inhibition Can Improve DR Severity

BL, baseline; DR, diabetic retinopathy; M, month; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; Q4W, every 4 weeks; VEGF, vascular endothelial growth factor.
But…How Do These Patients Behave After Monthly “Induction” Therapy Ends and Less Aggressive Treatment is Started?"

• How do these eyes behave compared with untreated eyes with the same DR severity?
• Which eyes are more prone to DRSS instability with intermittent dosing?

DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score.
RISE/RIDE: OLE Study

1:1:1 randomization of patients with DME
N = 759 (1 eye per patient)

Sham injection (n = 257)
Ranibizumab 0.3 mg (n = 250)
Ranibizumab 0.5 mg (n = 252)

Crossover

Ranibizumab 0.5 mg
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg

Primary endpoint

Pre-defined PRN criteria:
- DME on OCT
- Worsening of ≥ 5 ETDRS letters at M36 due to DME
- Not based on DR severity

*The study finished early (as prespecified) when ranibizumab was approved by the US Food and Drug Administration for DME; most patients did not have follow-up through M60.
BL, baseline; DME, diabetic macular edema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; ETDRS, Early Treatment Diabetic Retinopathy Study; M, month; OCT, optical coherence tomography; OLE, open-label extension; PRN, pro re nata.
RISE/RIDE: OLE Study

"New Baseline" at M36

End of Study at M48

- 367/500 patients from RISE/RIDE OLE with evaluable DRSS data at both M36 and M48
- BL (M0) and M36 ocular characteristics were compared with DRSS response and injection frequency from M36 to M48
  - **Maintained**: At M48, DRSS improved or maintained from M36 DRSS
  - **Returned to BL**: At M48, DRSS worsened but not beyond BL DRSS
  - **Worsened**: At M48, DRSS worsened beyond BL DRSS

Pre-defined PRN criteria:
- DME on OCT
- Worsening of ≥ 5 ETDRS letters at M36 due to DME
- **Not based on DR severity**

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BL, baseline; DME, diabetic macular edema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; ETDRS, Early Treatment Diabetic Retinopathy Study; M, month; OCT, optical coherence tomography; OLE, open-label extension; PRN, pro re nata.
Do Patients With Improved Retinopathy Behave Similar to Patients With “Native” Retinopathy?

Improved to ≤ 43 DRSS by end of RISE/RIDE (“induced” ≤ 43)

Started RISE/RIDE ≤ 43 DRSS and randomized to sham (“native” ≤ 43)

DRSS, Diabetic Retinopathy Severity Score.
Compare the Course of DR Over 12 Months for 2 Groups of Patients With Mild/Moderate NPDR

DME, diabetic macular edema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; M, month, NPDR, nonproliferative diabetic retinopathy; OLE, open-label extension..
Patients With “Induced” DRSS ≤ 43 More Likely to Worsen Over 1 Year Than Control Patients With “Native” DRSS ≤ 43 at BL

Positive change in DRSS indicates DR worsening; negative change in DRSS indicates DR improvement.

a Limited to patients with DR data at extension baseline (M36) and M48.

b All sham treated eyes enrolled in RISE/RIDE with DR data at BL and M12.

BL, baseline; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; M, month
What Can We Learn From Individual Outcomes During OLE by Comparing Patients with “Native” Versus Those With “Induced” NPDR?

NPDR, nonproliferative diabetic retinopathy; OLE, open-label extension.
DRSS Changes in Patients Receiving Ranibizumab in RISE/RIDE and OLE

How to Read the Plot

Each bar represents an individual patient, and patients are ordered from left (those with the greatest worsening) to right (those with the greatest improvement) from the selected BL.

n = 62

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; OLE, open-label extension.
The “Native” Mild NPDR Appears to be More Stable Than the “Induced” NPDR

“Native” ≤ 43 (Sham Treated)  
“Induced” to ≤ 43 (Ranibizumab Treated)

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; NPDR, nonproliferative diabetic retinopathy.
Patients With “Induced” Mild NPDR: DR Severity Changes Before and After M36

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; NPDR, nonproliferative diabetic retinopathy.
Patients With “Induced” Mild-to-Moderate NPDR: DR Severity Changes Before and After M36

Half of patients maintained ≥ 2-step improvement 4 years after RIDE/RISE

Half of patients maintained ≥ 2-step improvement 4 years after RIDE/RISE

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; NPDR, nonproliferative diabetic retinopathy.
Patients With “Induced” Mild-to-Moderate NPDR: DR Severity Changes Before and After M36

- Patients who worsened by 1 or 2 steps from M36–M48 improved by ≥ 2 steps from BL to M36
- Net stable DR over 4 years

BL, baseline; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; M, month; NPDR, nonproliferative diabetic retinopathy.
Patients With “Induced” Mild-to-Moderate NPDR: DR Severity Changes Before and After M36

- These patients worsened by ≥ 3 steps during OLE
- Most unstable phenotype
  - Great potential to improve with a propensity to relapse

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; NPDR, nonproliferative diabetic retinopathy; OLE, open-label extension.
Patients With “Induced” Mild-to-Moderate NPDR: DR Severity Changes Before and After M36

Many of these patients started with PDR (hatched bars)

46% (6/13)
13% (4/31)
9% (4/46)

Change in DRSS
Worsening (1 to 10)
Improvement (−1 to −10)

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.
What if we look at a broader patient population?

- Not just those eyes that improved to mild/moderate NPDR during RISE/RIDE

- How does BL DR severity impact changes in DRSS with regular treatment, followed by intermittent treatment?
Patients Received an Average 4–5 Ranibizumab Injections During OLE, Regardless of BL DRSS

This analysis includes 167 patients from OLE who were randomized to ranibizumab treatment during RISE/RIDE, and who did not have DRSS better than 35, or the presence of PRP at baseline.

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; OLE, open-label extension.
DRSS Changes in Patients Receiving Ranibizumab with Baseline PDR Were the Most Unstable Over RIDE/RISE and OLE

This analysis includes 167 patients from OLE who were randomized to ranibizumab treatment during RISE/RIDE, and who did not have DRSS better than 35, or the presence of PRP at baseline.

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month; OLE, open-label extension.
Conclusions

• The majority of ranibizumab-treated patients were able to improve or maintain their DRSS with less-than-monthly treatment
  • Some minimum treatment may be necessary to maintain DRSS improvement

• Regardless of BL DRSS, patients received an average of 4–5 injections during OLE
  • Continuous long-term monitoring and treatment may be necessary to maintain DRSS stability

• More severe DR at BL may be indicative of more unstable DRSS changes with intermittent dosing

• Small patient sample is an important limitation of this analysis

BL, baseline; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; OLE, open-label extension.
Instability in DRSS in Sham-Treated Patients
Majority Improved or Maintained BL DRSS Through M12

- Without prior panretinal photocoagulation.

BL, baseline; DRSS, Diabetic Retinopathy Severity Score; M, month.
Majority of Patients Improved or Maintained Their DRSS From M36 to M48 on PRN Treatment

- 60% of patients improved or maintained their DRSS from M36 to M48.
- 58% of patients did not experience any worsening.
- 50% of patients with baseline DRSS of 60-75 maintained their condition.

Baseline DRSS:
- N = 67 for baseline 35/43
- N = 80 for baseline 47/53
- N = 20 for baseline 60-75

*Without prior panretinal photocoagulation.

DRSS response was defined as ≥ 0 step improvement from M36 to M48 (improved or maintained) or ≥ 1 step DRSS worsening from M36 to 48 (worsening).

DRSS, diabetic retinopathy severity score; M, month; OLE, open-label extension; PRP, panretinal photocoagulation.