HAS THE TIME COME TO RE-EVALUATE THE TREATMENT PARADIGM FOR DIABETIC RETINOPATHY?

Quan Dong Nguyen, MD, MSc¹; Lauren F. Hill, MSc²; and Ivaylo Stoilov, MD²

¹ Byers Eye Institute, Stanford University, Palo Alto, CA; ² Genentech, Inc., South San Francisco, CA

Presented at the 53rd Annual Scientific Meeting | Retina Society 2020 VR | September 21–22, 2020
DISCLOSURES

• Financial disclosures
  • QDN: Consultant/Advisor: Bayer, Genentech, Inc., Regeneron, Santen
    • Stanford University, the employer of Dr Nguyen, has received research support from Genentech, Inc., Regeneron, and Santen
  • LFH: Consultant: Aerpio, Alimera, Genentech, Inc., PolyPhotonix, Recens Medical
  • IS: Employee/Stockholder: Genentech, Inc.

• Study disclosures
  • This study includes research conducted on human subjects
  • Institutional Review Board approval was obtained prior to study initiation
  • Funding was provided by Genentech, Inc., a member of the Roche Group, for the study and third-party writing assistance, which was provided by Karina D. Hamilton-Peel, PhD, CMPP, of Envision Pharma Group
**Key Takeaways**

- The index study examined whether the current evidence supports a paradigm shift towards earlier intervention in patients with diabetic retinopathy (DR).

- Analyses of real-world data have associated proliferative diabetic retinopathy (PDR) with the development of sustained blindness in clinical practice.

- Meanwhile, landmark trials showed that patients with moderately severe or severe NPDR were vulnerable to DR progression without treatment, and more likely to achieve DR improvement with anti-VEGF therapy.

- Given the trend towards greater mean vision gains with greater DR improvement in RIDE/RISE, these data suggest that the time has come to consider earlier intervention to delay progression towards PDR.

DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.
Early Intervention Is Associated With Delayed Disease Progression and Improved Patient Outcomes Across the Medical Field

Multiple Sclerosis\(^1,2\)

![Diagram showing disease progression and treatment timelines for Multiple Sclerosis and Rheumatoid Arthritis]

Rheumatoid Arthritis\(^3\)

Cardiovascular Disease\(^4\)


DMARD, disease-modifying antirheumatic drug.
DO CLINICAL TRIAL AND REAL-WORLD EVIDENCE SUPPORT A PARADIGM SHIFT TOWARDS EARLIER INTERVENTION IN PATIENTS WITH DR?
PROGRESSION TO SUSTAINED BLINDNESS IN CURRENT CLINICAL PRACTICE: AN IRIS® REGISTRY (INTELLIGENT RESEARCH IN SIGHT) ANALYSIS

- **Aim:** To characterize the development of sustained blindness in patients with DR
- **Method:** Retrospective analysis of the AAO IRIS Registry
  - First comprehensive clinical data registry for US-based eye care providers
  - Developed to drive quality improvement in ophthalmic care

**Patient selection:** January 1, 2013 to December 30, 2017

**Study period:** all available data to December 31, 2017

Nguyen QD et al. Presented at: American Diabetes Association 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA (manuscript in development).
AAO, American Academy of Ophthalmology; DR, diabetic retinopathy.
IRIS Registry Analysis

AAO IRIS Registry
1/1/2013–12/31/2017
N = 821,360

Include eyes in patients ≥ 18 years of age with:

- **Newly diagnosed DR**
  - ≥ 18 months with no documented DR followed by
    ≥ 2 confirmed diagnoses of DR in study eye
- **Good vision**
  - ≥ 2 VA readings of ≤ 20/40 before or up to 3 months post index date, including 1 VA reading of ≤ 20/40 ≤ 3 months from index

Exclude eyes with:

- Diagnosis of DR before index date
- Any history of retinal conditions (wet or dry AMD, GA, RVO, mCNV, DME, RD, VH, NVG)
- Any history of retinal treatment (PRP, focal laser, anti-VEGF, intravitreal steroids, vitrectomy, RDR)

N = 53,535

Event of interest: development of sustained blindness during follow-up

- ≥ 2 VA readings of 20/200 or worse ≥ 3 months apart
- No improvement beyond 20/100 after first 20/200 reading
- Time of event of sustained blindness = date of first VA reading of 20/200 or worse

Nguyen QD et al. Presented at: American Diabetes Association 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA (manuscript in development). AAO, American Academy of Ophthalmology; AMD, age-related macular degeneration; DME, diabetic macular edema; DR, diabetic retinopathy; GA, geographic atrophy; mCNV, myopic choroidal neovascularization; NVG, neovascular glaucoma; PRP, panretinal photocoagulation; RD, retinal detachment; RDR, retinal detachment repair; RVO, retinal vein occlusion; VA, visual acuity; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage.
IRIS Registry: Higher Probability of Developing Sustained Blindness in Patients Diagnosed With Severe NPDR or PDR

Log-rank $P < 0.0001.$

Nguyen QD et al. Presented at: American Diabetes Association 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA (manuscript in development).

DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.
RIDE/RISE: Anti-VEGF Therapy Slowed Progression of Retinal Nonperfusion Over 24 Months

Eyes Without Retinal Nonperfusion, %

- Sham (n = 228)
- RBZ 0.3 mg Q4W (n = 213)
- RBZ 0.5 mg Q4W (n = 225)

56.9%
75.1%
74.4%

*P < 0.001 versus sham.
Q4W, every 4 weeks; RBZ, ranibizumab; VEGF, vascular endothelial growth factor.
RIDE/RISE: Rates of DR Progression Were Greatest in Untreated Fellow Eyes With Moderately Severe or Severe NPDR (DRSS 47–53)

Analyses excluded eyes with prior panretinal photocoagulation at baseline; RBZ 0.3 mg and 0.5 mg treatment arms combined.

Bakri SJ et al. Presented at: 37th Annual Meeting of the American Society of Retina Specialists; July 26-30, 2019; Chicago, IL (manuscript in development).

DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; RBZ, ranibizumab.
RIDE/RISE AND PANORAMA: HIGH RATES OF DR IMPROVEMENT WITH ANTI-VEGF THERAPY IN EYES WITH MODERATELY SEVERE OR SEVERE NPDR

Eyes with prior panretinal photocoagulation at baseline were excluded.


AFL, aflibercept; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; PRN, pro re nata (as-needed); Q4W, every 4 weeks; Q8W, every 8 weeks; Q16W, every 16 weeks; RBZ, ranibizumab; VEGF, vascular endothelial growth factor.

Baseline DR Severity

<table>
<thead>
<tr>
<th>DRSS 35–43</th>
<th>DRSS 47–53</th>
<th>DRSS 60–75</th>
<th>DRSS 47–53</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIDE/RISE¹</td>
<td>RIDE/RISE¹</td>
<td>RIDE/RISE¹</td>
<td>PANORAMA²</td>
</tr>
<tr>
<td>n = 71</td>
<td>86</td>
<td>30</td>
<td>133</td>
</tr>
<tr>
<td>1%</td>
<td>12%</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>10%</td>
<td>78%</td>
<td>31%</td>
<td>15%</td>
</tr>
<tr>
<td>16%</td>
<td>81%</td>
<td>36%</td>
<td>50%</td>
</tr>
<tr>
<td>10%</td>
<td>51%</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>16%</td>
<td>12%</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>10%</td>
<td>50%</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td>16%</td>
<td>16%</td>
<td>16%</td>
<td>10%</td>
</tr>
</tbody>
</table>
PROTOCOL I: RATES OF DR IMPROVEMENT WITH RBZ WERE NUMERICALLY GREATER IN EYES WITH MODERATELY SEVERE OR SEVERE NPDR OVER 5 YEARS

In eyes with NPDR (DRSS 35–43 or 47–53) at baseline, DR improvement was defined as an ≥ 2-step DRSS improvement versus baseline. In eyes with active proliferative DR (PDR; DRSS > 60) at baseline, DR improvement was defined as an ≥ 2-step DRSS improvement versus baseline, or regression to no PDR (DRSS ≤ 53 if no prior panretinal photocoagulation [PRP]; DRSS level 60 if PRP was present at study entry).


DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; RBZ, ranibizumab.

In eyes with NPDR (DRSS 35–43 or 47–53) at baseline, DR improvement was defined as an ≥ 2-step DRSS improvement versus baseline. In eyes with active proliferative DR (PDR; DRSS > 60) at baseline, DR improvement was defined as an ≥ 2-step DRSS improvement versus baseline, or regression to no PDR (DRSS ≤ 53 if no prior panretinal photocoagulation [PRP]; DRSS level 60 if PRP was present at study entry).


DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; RBZ, ranibizumab.

Analyses included study eyes randomized to monthly RBZ 0.3 mg and 0.5 mg at RIDE/RISE baseline (n = 468).

BCVA, best-corrected visual acuity; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; RBZ, ranibizumab.
CONCLUSIONS

- IRIS Registry analyses have associated PDR with the development of sustained blindness in current clinical practice.

- Landmark trials found that patients with moderately severe or severe NPDR (DRSS 47–53) are vulnerable to DR progression without treatment, and are more likely to achieve DR improvement with anti-VEGF therapy.

- Further analyses revealed a trend toward greater mean vision gains, with greater DR improvement among anti-VEGF–treated eyes in RIDE/RISE.

- These data raise the question of whether the time has come to re-evaluate therapeutic goals in DR management, including early intervention to delay progression towards PDR.

DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.