Open-Label Extension of RIDE and RISE Shows Improved Visual Outcomes Maintained Without Ranibizumab Retreatment

Written by Nicola Parry

Charles C. Wykoff, MD, PhD, Retina Consultants of Houston, Houston, Texas, USA, presented data from the open-label extension (OLE) study of the RIDE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus; NCT00473382] and RISE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus; NCT00473330] trials. The results demonstrated that almost one-fourth of participants in the OLE study maintained vision and retinal anatomy gains achieved during the RIDE and RISE trials without the need for additional ranibizumab injections.

According to Dr Wykoff, upon completion of the core 36-month RIDE and RISE trials, 66% (n = 500) of the 759 originally randomized patients enrolled in the OLE trial. Patients were then examined essentially monthly and treated with 0.5-mg ranibizumab injections on a PRN basis according to predefined retreatment criteria, including evidence of diabetic macular edema (DME) on optical coherence tomography.

There was a wide variation in the frequency of PRN ranibizumab injections during OLE, and 24.2% of patients required no injections (mean = 4.5 injections). Dr Wykoff indicated that the objective of this subanalysis was to further characterize this group of patients who received no injections during OLE and compare them with a group of patients who required many injections during OLE (> 7 annualized injections, or 17.6% of the OLE population).

Analysis of patient baseline and treatment characteristics from RIDE and RISE demonstrated that 10 particular characteristics correlated with ultimate treatment frequency during OLE (Table 1).

With respect to baseline characteristics, the duration of clinically significant DME was approximately 10 months shorter in patients receiving no ranibizumab injections during OLE. These patients also had better vision (approximately 4 more letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart), better retinal anatomy (approximately 85 µm less mean

Table 1. Characteristics That Correlated With Treatment Frequency During Open-Label Extension

Baseline	Duration of clinically significant diabetic macular edema
	Best corrected visual acuity
	Central foveal thickness
	Diabetic retinopathy severity
Treatments received	Number of total lasers
	Number of rescue lasers
Treatment response	Best corrected visual acuity
	Central foveal thickness
	Diabetic retinopathy severity
	HbA_{1c}
	Fluorescein angiography leakage

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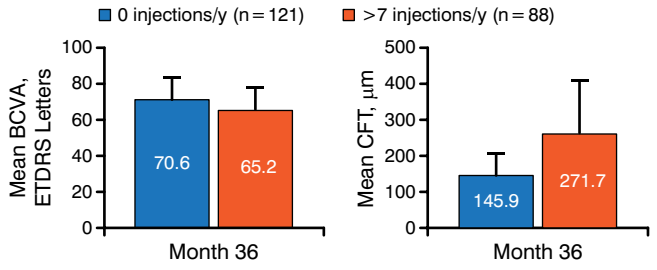
Figure 1. Visual Gains and Central Foveal Thickness During Open-Label Extension



BCVA, best corrected visual acuity; CFT, central foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

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central foveal thickness [CFT] related to DME), and less severe diabetic retinopathy (DR), including less proliferative DR.

From a treatment perspective, patients who required no ranibizumab injections during OLE required fewer laser applications during the RISE/RIDE trials than those who received many injections during OLE.

With respect to treatment response during RISE/RIDE, 5 characteristics correlated with ultimate treatment frequency during OLE. Patients who required no ranibizumab injections had better vision (approximately 5 more ETDRS chart letters) and better retinal anatomy (approximately 125 µm less mean CFT related to DME) at month 36 (Figure 1).

More patients who received no injections during OLE experienced a 2-step greater improvement in DR severity at 36 months (40% vs 19%). These patients also experienced more improvement in the area of dye leakage on fluorescein angiography, with a difference of >2 mean disc areas of improvement at 36 months compared with patients receiving >7 injections during OLE. Finally, there was a slight negative correlation between HbA_{1c} levels at 36 months and the need for ranibizumab reinjection during OLE; HbA_{1c} levels slightly increased from baseline to 36 months in patients who required no injections, whereas they remained stable in those who received >7 injections.

Dr Wykoff noted that although OLE was designed to continue for 2 years, the trial ended after approval of ranibizumab by the US Food and Drug Administration for the treatment of DME. In summary, he noted that during OLE, patients who required no ranibizumab injection were characterized by less severe ocular diabetic disease at baseline and a better response to ranibizumab during the core RIDE and RISE trials.

Ranibizumab 0.5 mg Safe and Effective for Treatment of DME

Written by Brian Hoyle

Marco Zarbin, MD, PhD, University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey, USA, described a post hoc analysis of 5 studies of the humanized monoclonal antibody ranibizumab directed against vascular endothelial growth factor (VEGF)-A in the treatment of diabetic macular edema (DME) [Gaudreault J et al. *Retina*. 2007]. The analysis focused on the arterial thromboembolic events (ATEs) associated with ranibizumab that have been reported in controlled clinical trials.

VEGF suppression in patients with cancer increases the risk of hypertension and ATEs [Semeraro F et al. *Expert Opin Drug Saf*. 2014], but the situation is less clear in patients being treated for DME. The analysis looked at the long-term incidence (up to 3 years) of ATEs in patients with DME who were receiving ranibizumab.

Data from 5 studies collectively involving 881 patients were pooled and analyzed. The 1-year RESOLVE study used 0.3, 0.5, 0.6, and 1.0 mg ranibizumab PRN [Massin P et al. *Diabetes Care*. 2010]. The remaining studies—the 1-year RESTORE and REVEAL studies [Mitchell P et al. *Ophthalmology*. 2011], the 2-year RESTORE extension study [Lang GE et al. *Ophthalmology*. 2013], the 2-year RETAIN study [NCT01183468], and the 3-year RESTORE extension study [Schmidt-Erfurth U et al. *Ophthalmology*. 2014]—used ranibizumab 0.5 mg PRN.

The baseline characteristics—age, sex, ethnicity, hemoglobin A_{1c}, and duration of diabetes—across the 5 trials were similar after exclusion of patients with prior ATEs.

In the RESOLVE, RESTORE, and REVEAL trials, the 1-year incidence of ATEs was similar in the ranibizumab arm (2.9%; n = 350 in the treatment arm) and in the control arm (3.8%; n = 287 in the sham/laser arm). The annualized proportion of nonmyocardial ATEs in ranibizumab-treated patients was 1.7% annually at 1 year, 2.8% annually at 2 years (RESTORE extension and RETAIN trials), and 1.6% annually at 3 years (RESTORE extension trial). The annualized rate of myocardial infarction was 1.7%, 0.6%, and 0.0% annually at 1, 2, and 3 years, respectively. The incidence of vascular death in patients receiving ranibizumab 0.5 mg was similar to controls, and was comparable in patients treated for 2 or 3 years.

The analysis has several limitations. The 5 studies were not powered to detect differences in safety events. Data are also insufficient on the use of anti-VEGF drugs