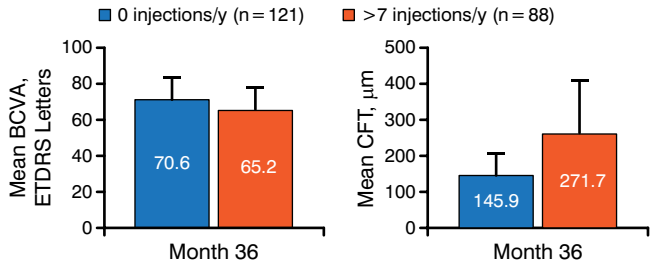
Figure 1. Visual Gains and Central Foveal Thickness During Open-Label Extension



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

in patients at high risk of DME, which reflects a tendency to exclude patients that are predisposed to treatment complications. For example, data on file with Novartis indicate that 3.4% of the patients in DME trials treated with ranibizumab 0.5 mg had experienced a prior stroke or transient ischemic attack. More knowledge on the patients who are at greater risk of complications is warranted.

Such real-world evidence will be forthcoming in the LUMINOUS study [NCT01318941] being coordinated by Novartis, which has enrolled 30 000 patients at approximately 500 sites from >40 countries globally. The prospective 5-year observational study will evaluate the long-term safety and efficacy of ranibizumab in real-world clinical practice.

For now, there is no evidence to suggest any difference in safety between ranibizumab 0.5 mg and the control (sham/laser) in the 5 studies.

Methodological Shortcomings Revealed in Clinical Guidelines for Primary Open-Angle Glaucoma

Written by Brian Hoyle

A study examining 3 separate clinical practice guidelines governing primary open-angle glaucoma found that all 3 sets of guidelines require improvements, stated Annie Wu, MD, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA.

Glaucoma affects about 60.5 million people globally and is the second leading cause of blindness [Quigley HA, Broman AT. *Br J Ophthalmol.* 2006]. Although rigorous clinical practice guidelines are necessary for glaucoma, there are obstacles that can color the rigor of guidelines, including conflict of interest and quality of the evidence [Kung J et al. *Arch Intern Med.* 2012; Ransohoff DF et al. *JAMA*. 2013].

The present study evaluated the quality of guidelines for primary open-angle glaucoma published in recent years by the American Academy of Ophthalmology (AAO) [AAO Glaucoma Panel, Primary Open-Angle Glaucoma Preferred Practice Patterns, 2010], Canadian Ophthalmological Society (COS) [COS, *Can J Ophthalmol.* 2009], and the National Institute for Health and Care Excellence (NICE) [National Collaborating Center for Acute Care. Glaucoma: Diagnosis and management of chronic open-angle glaucoma and ocular hypertension. London (UK), 2009].

Four evaluators independently appraised each set of guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool [Brouwers M et al. *CMAJ.* 2010]. AGREE II contains 6 domains: Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence. The overall assessment score across all domains uses a 7-point scale; a score of 7 indicates 100% adherence to the particular guideline.

Application of AGREE II–produced scores ranged from 28% to 85% for the AAO guidelines, 51% to 96% for the COS guidelines, and 55% to 97% for the NICE guidelines. Scope and Purpose was the strongest domain for all 3 sets of guidelines. Clarity of Presentation was a strong domain for the COS and NICE guidelines. The

Table 1. Comparison of AGREE II Scores in Evaluation of Glaucoma Guidelines

Agree II Domain	AAO	COS	NICE
Scope and Purpose, %	85	86	93
Stakeholder Involvement, %	28	51	79
Rigor of Development, %	63	72	92
Clarity of Presentation, %	78	96	97
Applicability, %	58	67	92
Editorial Independence, %	64	77	55
Overall assessment	**4.75/7.0**	**5.50/7.0**	**6.25/7.0**

AAO, American Academy of Ophthalmology; COS, Canadian Ophthalmological Society; NICE, National Institute of Health and Care Excellence.