MODULE 10.2
Clinical Studies and Treatment Data - RESOLVE

RESOLVE[1]

Study Name	Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study*)
Purpose of study	To determine the safety and efficacy of ranibizumab in diabetic macular edema (DME) involving the foveal center
Study authors	Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, Mitchell P, Sharp D, Wolf-Schnurbusch UEK, Gekkieva M, Weichselberger A, Wolf S.
Published in	
Study also known as	RESOLVE
Subsequent studies	N/A

Study Overview

RESOLVE was a phase 2, 12-month, multicenter, sham-controlled, double-masked study conducted at centers in Australia, Korea, and throughout Europe that enrolled 151 patients with a central retinal thickness (CRT) of at least 300 µm, and a best-correct visual acuity (BCVA) of 73-39 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and well-controlled systemic diabetes.[1] Exclusion criteria included previous panretinal laser photocoagulation within the previous 6 months; people who had undergone grid/central laser were also excluded unless the laser burns were considered mild and at least 1000 µm from the foveal center.

Patients were randomly assigned to intravitreal ranibizumab 0.3 mg (n = 51), intravitreal ranibizumab 0.5 mg (n = 51) or sham injection (n = 49). In this study, patients underwent a 3-month dose-loading phase after which treatment could be stopped or reinitiated with rescue laser photocoagulation. After the first month, dose-doubling in the 0.5-mg arm was permitted.

Dose-doubling allowed for any arm to be doubled by increasing the injection volume from 0.05 to 0.1 mL if the CRT remained more than 300 µm, was 225 µm, and the reduction in retinal edema from the previous assessment was <50 µm. The study authors noted that once dose-doubling occurred, subsequent administrations remained at the 0.1-mL levels (or 0.6 mg or 1.0 mg). Throughout this study, therefore, the results of the ranibizumab 0.3-mg arm are really 0.3 mg to 0.6 mg, and the results of the ranibizumab 0.5-mg arm are really 0.5 mg to 1.0 mg. However, if treatment had been withheld for more than 45 days, retreatment was initiated at the original dose level (0.3 mg or 0.5 mg).

The primary outcome was the mean average change in BCVA over 12 months. RESOLVE defined this change as the difference between BCVA at baseline and the average of BCVA values measured at months 1 to 12. Other analyses have found this to be a more stringent endpoint because it incorporates the treatment effect over the entire treatment period rather than just comparing 2 individual points (ie, baseline and final study follow-up).[2] Secondary outcomes included the mean change in CRT.

At month 12, mean ± SD BCVA improved from baseline by 10.3 ± 9.1 letters with ranibizumab and declined by 1.4 ± 14.2 letters with sham ($P < .0001$). Mean CRT reduction was 194.2 ± 135.1 µm with ranibizumab and 48.4 ± 153.4 µm with sham ($P < .0001$). Gain of ≥10 letters BCVA from baseline occurred in 60.8% of ranibizumab and 18.4% of sham eyes ($P < .0001$).[1] Safety data were consistent with previous studies of intravitreal ranibizumab. Only 5 eyes (4.9%) in the pooled ranibizumab groups needed rescue laser therapy, compared with 17 eyes (34.7%) in the sham group. See Figures 1 and 2, with pooled ranibizumab data.

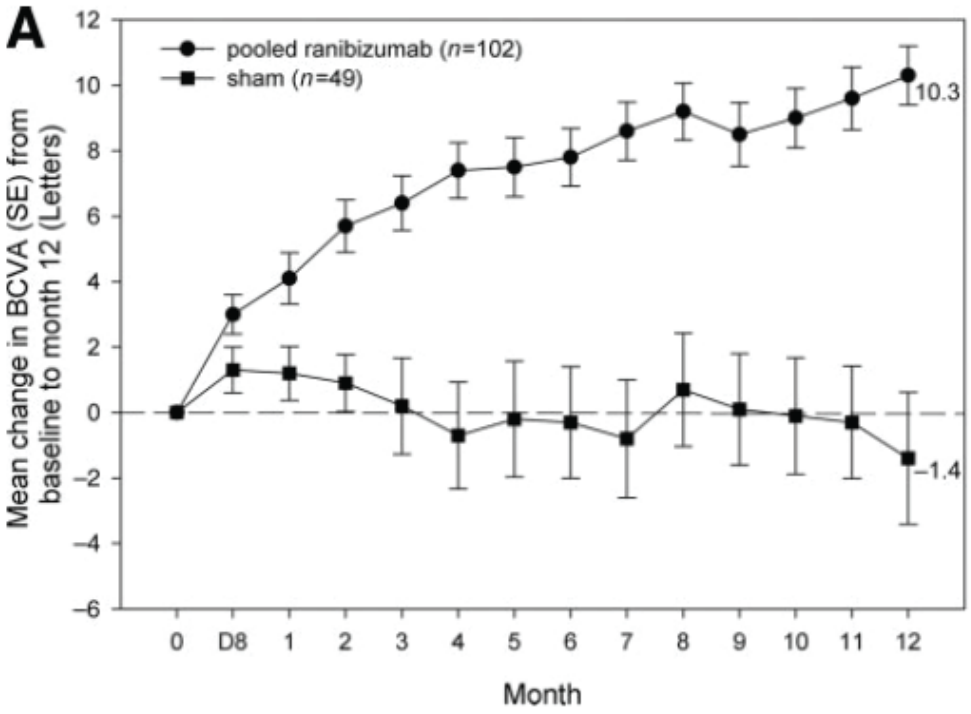

Figure 1: Mean change from baseline to month 12 in BCVA.

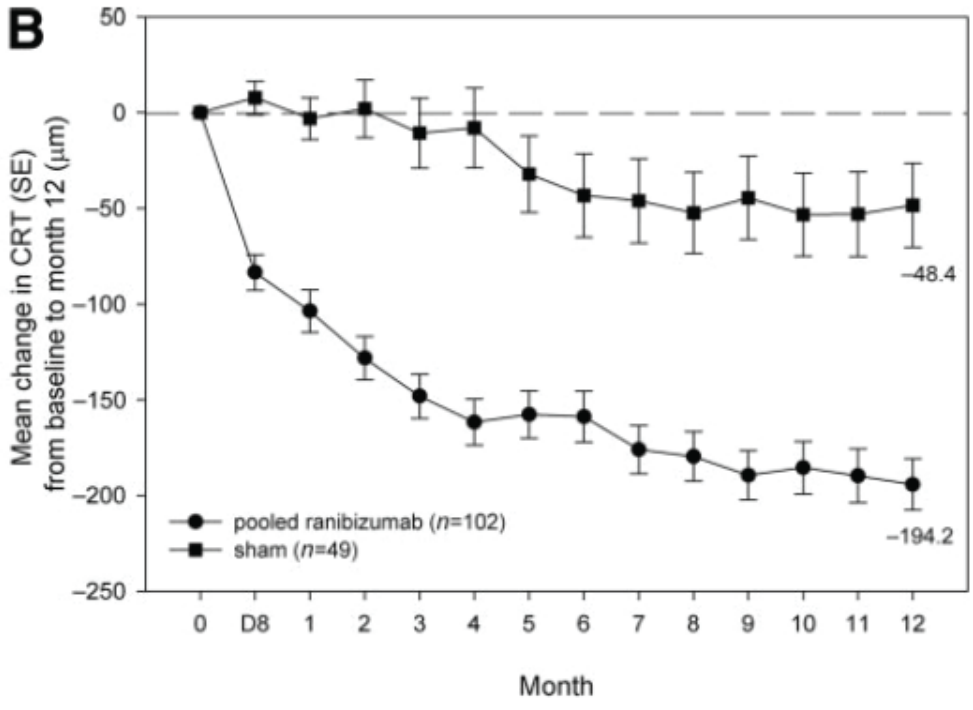

Figure 2: Mean change from baseline to month 12 in central retinal thickness.

Study implications

This was one of the first studies to evaluate ranibizumab on its own compared to sham for the treatment of DME.

The study authors acknowledged the need for individualized treatment regimens given the nature of the systemic disorder and variability in patients with the ocular manifestations. The RESOLVE study allowed for discontinuation/re-initiation of therapy and for variability within the treatment arms to more closely represent clinical practice. However, "unlike clinical practice, the visual acuity/CRT criteria adopted in the study were stringent to increase the likelihood of patient benefit."[1]

This is the first study to allow dose-doubling in any treatment arm, but the study was not powered to evaluate the effect of dose-doubling. Because of the variability in dosing, the study authors pooled the ranibizumab groups and noted the results were representative of those treated with 0.5mg injections.

Key Take Home points

- Ranibizumab was well tolerated over 12 months with a safety profile comparable to that observed in other diseases (neovascular age-related macular degeneration, for example).
- Dose doubling did not seem to have an effect on the visual or anatomic outcomes of ranibizumab, but the study was not designed to quantify that information.

References

1. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care.* 2010;33(11):2399-2405.

2. Bandello F, Cunha-Vaz J, Chong NV, et al. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. *Eye (Lond).* 2012;26(4):485-493.