MODULE 10.1
Clinical Studies and Treatment Data: - READ

READ - Clinical Study[1]

Study Name	Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study
Purpose of study	To compare ranibizumab with focal/grid laser and to the combination of both in treating diabetic macular edema (DME)
Study authors	Nguyen QD, Shah SM, Heier JS, et al for the READ-2 Study Group
Published in	*Ophthalmology.* 2010;117:2146-2151.
Study also known as	READ-2
Subsequent studies	Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology.* 2010;117:2146-2151. Do DV, Nguyen QD, Khwaja AA, et al. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. *JAMA Ophthalmol.* 2013;131:139-145.

Study Overview

The Ranibizumab for Edema of the Macula in Diabetes 2 (READ-2)[1] study was a prospective, randomized, interventional trial that compared ranibizumab with focal/grid laser and the combination of both for the treatment of patients with diabetic macular edema (DME). The study was conducted at 14 centers throughout the United States; both the 6-month (primary outcomes) and the 2-year outcomes have been reported.[2,3] As with other studies, the main outcome measure was the mean change from baseline in best-corrected visual acuity (BCVA), with secondary end points including changes in foveal thickness from baseline to month 6 and the percentage of patients with substantially decreased foveal thickness.

The study enrolled 126 patients, all with a BCVA of 20/40 to 20/320, a central subfield thickness of more than 250 µm, and a hemoglobin A1C (HbA1c) of at least 6% within the previous 12 months. Either form of diabetes was allowed, as long as confirmed DME was present. Patients were evenly randomized [each arm enrolled 42 patients to either ranibizumab 0.5 mg at baseline, months 1, 3, and 5 (Group 1); to focal/grid laser at baseline and month 3 if needed (Group 2); and to ranibizumab 0.5mg and focal/grid laser at baseline and month 3 (Group 3)].[2] After 6 months, all patients were eligible to receive ranibizumab, with Groups 1 and 2 being evaluated every 2 months. Group 3 was evaluated every 3 months and could receive either ranibizumab and laser or ranibizumab alone. Group 2 was further randomized to ranibizumab or laser, presuming laser had not been performed in the prior 3 months.[3]

After 2 years, Group 1 had a mean 5.3 injections, Group 2 had a mean 4.4 injections, and Group 3 had a mean 2.9 injections (of a possible 9 injections in each group). Group 3 had a mean of 2.3 laser treatments from the 6-month time point through month 24; the other two groups had a mean of fewer than 1 laser treatment.

Other key results include a statistically significant larger gain in number of ETDRS letters read at 4 m in Group 1 than in the other groups. More impressive, perhaps, was the percentage of patients with a 3-line gain in Group 1 (22%) compared to Group 2 (8%) or Group 3 (0%).

Foveal thickness also improved in all groups, but initially decreased substantially in Group 1 before increasing at months 12 and 24. Conversely, there was a steady decrease in central foveal thickness during the 24 months in Groups 2 and 3. Further, the changes in foveal thickness in Groups 2 and 3 were statistically significant when compared to Group 1.[3] It is interesting to note, however, that baseline foveal thickness was greater in Group 3 (262.5 µm), followed by Group 2 (227.6 µm), and Group 1 (210 µm) and in the first 6 months, all groups had statistically significant decreases in thickness.[2]

Systemically, there were no differences noted in blood pressure within or among the groups at any time point; the majority of ocular adverse events occurred in Group 2, followed by Group 3. In both these groups, the reported vitreous hemorrhage resolved by 6 months.[2]

Study Implications

A key differentiator in READ-2 from other studies is that investigators gave injections every 2 months in the ranibizumab group and in the combination group, and patients received focal laser 1 week after their injection. By 2 years, the visual outcomes were similar among the 3 treatment arms, but anatomical outcomes were better with fewer injections. The study authors suggested that adjunctive laser treatment causes distortion of retinal architecture and retinal anatomy; however, these differences did not correlate with decline in visual function.[3]

In READ-2, the primary endpoint results showed that ranibizumab by itself (as monotherapy) resulted in better visual outcomes than laser alone or than ranibizumab plus laser. However, the sample size was not large enough to conclusively determine if combined treatment (ranibizumab + laser) is superior to either treatment regimen on its own in the initial study. But the 2-year results found VA gains were similar between the ranibizumab and combination therapy groups (approximately 7 letters), and both were superior to laser alone.[3]

After the initial 6-month study, most patients in the extended 2-year study were treated with only ranibizumab (n = 33 in Group 1, n = 34 in Group 2, and n = 34 in Group 3). In this group of patients, when ranibizumab was used in combination with focal or grid laser, the residual edema was reduced, as was the need for frequent injections. Continued follow-up (through 2 and 3 years)[2] also showed that improvement in central retinal thickness was similar among the groups, as determined by optical coherence tomography (OCT). In the longest follow-up (3 years),[1] 50% of the patients in the original ranibizumab group met the retreatment criteria at more than 6 visits and needed continued treatment; only 18% required no further treatment by month 36. After 6 visits, only 8% of the combination group met the retreatment criteria, and 46% did not need treatment by month 36. These findings, however, often do not reflect that of a real-world setting; most retinal specialist believe their patients will require anti-VEGF treatment indefinitely.[4]

Some retinal specialists may argue that focal laser to well-defined microaneurisms that are clear foci of leakage and exudate can decrease the need for frequent injections. Most retinal specialists agree that focal laser alone still has a role for select patients in DME. However, studies like READ-2 and RIDE/RISE do not find laser alone to be superior in most patients compared to ranibizumab or combination therapy groups. The 6-month READ-2 study authors suggested more aggressive dosing would be recommended - the every-other-month treatment regimen (after dose-loading) led to a 50% reduction in edema. As was subsequently shown in RIDE/RISE, however, monthly dosing led to a much greater amount of edema reduction.

The READ-2 results, coupled with those from RIDE/RISE, led the FDA to approve ranibizumab for the treatment of DME. These 2 studies have changed practice patterns amongst retinal specialists today. Before the advent of OCT and anti-VEGF medications, well-defined criteria that indicated clinically significant macular edema (CSME) guided the decision to treat with the gold standard of laser. Currently, studies like READ-2 and RISE/RIDE have proven that anti-VEGF medications are more effective than laser alone. Furthermore, OCT has proven to be more sensitive to the detection of retinal edema than the criteria for CSME. A paradigm shift in the evaluation and treatment of DME has taken place over the past 15 years. Practical decision making among retinal specialists about when to treat DME is based on OCT findings and visual acuity, not CSME criteria. Additionally, first-line therapy for DME patients is intravitreal injections with anti-VEGF medication, not focal/grid laser alone.

Take Home Points

- Treatment with ranibizumab or combination (laser + ranibizumab) is superior to laser therapy alone
- Treatment with ranibizumab or combination results in less frequent treatments (fewer patients meeting treatment requirements) over a 36-month period
- An impressive 3-line gain in VA was achieved in the ranibizumab only group

References

1. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology.* 2010;117:2146-2151.

2. Do DV, Nguyen QD, Khwaja AA, et al. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. *JAMA Ophthalmol.* 2013;131:139-145