

Anti-VEGF Treatment for Diabetic Macular Edema

Aggressive treatment helped to control DME in the third year of follow-up in the READ-2 study.

BY THOMAS G. CHU, MD, PhD

Diabetic macular edema (DME) is a common cause of visual loss in individuals with diabetes mellitus.¹ Recently, pharmacologic blockade of vascular endothelial growth factor (VEGF) has shown promise as a primary treatment for DME in several studies.

The READ-2 study was a phase 2, multicenter randomized prospective clinical trial comparing the effectiveness of intravitreal injection of the anti-VEGF agent ranibizumab (Lucentis, Genentech) 0.5 mg, focal/grid laser treatment alone, or a combination of ranibizumab and focal/grid laser treatment, in subjects with diabetic macular edema (DME).

The primary endpoint of the READ-2 study, change in best corrected visual acuity (BCVA) from baseline to month 6, has already been reported,² as have data from 2-year follow-up in the study.³ The 36-month results of the READ-2 study were recently presented.⁴ This article reviews some of the previously published data and summarizes the 36-month data.

STUDY DESIGN AND POPULATION

In the READ-2 Study, investigators at 14 centers throughout the United States enrolled 126 treatment-naïve patients with DME, who were randomly assigned to 1 of 3 treatment protocols: ranibizumab alone (group 1), focal laser (group 2), or ranibizumab in combination with focal laser (group 3). The primary outcome was the change in BCVA from baseline to month 6.

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In group 1, patients received 0.5 mg ranibizumab injection at baseline and months 1, 3, and 5. The primary outcome was at month 6, and subsequently, at examinations every 2 months out to 24 months, patients were eligible to be retreated based on retreatment criteria, principally a finding of central foveal thickness greater than 250 μ m on optical coherence tomography (OCT). In group 2, patients received laser treatment at baseline and month 3; after the primary outcome at month 6, patients were followed with the option of receiving ranibizumab or laser treatment at the discretion of the investigator. In group 3, patients received both laser and ranibizumab at baseline and month 3; again, after the primary outcome at month 6, ranibizumab or laser treatment was given at the investigator's discretion if retreatment criteria were met.

The study was originally designed to last 24 months, but there was an amendment to the trial, extending follow-up from month 24 through month 36. During this 3rd year, patients were evaluated every month instead of every 2 months, and in all 3 arms patients were eligible to be treated with ranibizumab monthly if they met treat-

ment criteria. Patients in groups 2 and 3 could also receive laser treatment at the investigator's discretion.

The baseline characteristics of the 3 groups were mostly similar, although there was a smaller percentage of women in group 1 than in groups 2 and 3 (30.9%, 45.2%, and 47.6%, respectively). Mean Snellen equivalent visual acuity was similar in the 3 groups, at approximately 20/80, as was mean excess central foveal thickness on OCT, ranging from approximately 200 μ m to approximately 250 μ m. The degree of diabetic control as expressed by hemoglobin a1c readings was also similar across the groups.

6- AND 24-MONTH RESULTS

At the month 6 primary endpoint, as Nguyen and colleagues reported in 2009,² mean gain in BCVA was significantly greater in group 1 (+7.24 letters, $P = .01$) compared with group 2 (−0.43 letters), and the change in group 3 (+3.80 letters) was not statistically significantly different from group 1 or 2.

By month 24, as Nguyen and colleagues reported in 2010,³ about 80% of patients were retained in the trial. The mean number of injections given during the as-needed (prn) portion of the study from month 6 to month 24 was 5.3 in group 1 (of a possible 9), 4.4 in group 2 (of a possible 9), and 2.9 in group 3 (of a possible 6).

The improvement of BCVA seen in the ranibizumab-alone group was maintained to month 24, and with the availability of ranibizumab treatment from month 6 to month 24 the other 2 groups experienced improvement from the month 6 primary endpoint. The change from baseline BCVA at month 24 was +7.70 in group 1 ($n=33$), +5.10 in group 2 ($n=34$), and +6.80 in group 3 ($n=34$).

36-MONTH RESULTS

By 36 months there was a notable drop-off in patient enrollment, especially in group 2. From month 24 to month 36, 85% of patients were maintained in group 1 ($n = 28$), 65% in group 2 ($n = 22$), and 71% in group 3 ($n = 24$).

There was the potential for patients to receive as many as 12 monthly treatments with ranibizumab in the 3rd year of the study. The mean number of injections given during those 12 months was 5.4 in group 1, 3.2 in group 2, and 2.3 in group 3. The number of potential laser treatments that could be given was also 12, and there were a mean 0 laser treatments given in group 1, 2 in group 2, and 1 in group 3.

Further improvement in BCVA was seen at month 36 relative to month 24 in group 1 (+10.3 letters from baseline), and group 3 (+9.5 letters from baseline), but a decline in group 2 (+1.4 letters from baseline). Approximately one-third of patients in group 1 gained 3 lines (15 letters) or more of BCVA from baseline at

month 36, and about one-quarter in group 3, but less than 10% gained 3 lines or more in group 2.

Regarding anatomic results, there was an increase in the percentage of eyes with central foveal thickness less than 250 μ m in all 3 groups and a corresponding decrease in mean central foveal thickness in all 3 groups.

Few adverse events were seen in the study. One eye developed endophthalmitis, and there were no drug-related serious systemic adverse events.

CONCLUSION

At the primary 6-month endpoint of the READ-2 study, treatment with ranibizumab alone resulted in superior improvement in BCVA compared with laser treatment alone and combination therapy. During months 6 to 24, prn ranibizumab treatment, given with a possible frequency of every 2 months, resulted in maintenance of BCVA benefits.

The change in protocol, allowing monthly ranibizumab or laser treatment from month 24 to 36, resulted in improvement in BCVA in groups 1 and 3 and a decline in group 2. Care should be taken in drawing conclusions from the 36-month results of this study due to the limitations of small sample size and the higher dropout rate seen in group 2.

This study adds to the emerging evidence indicating that VEGF inhibition is beneficial in the treatment of patients with DME. No serious systemic adverse effects of ranibizumab were observed in the study.

Some patients may require more frequent anti-VEGF injections to optimally control DME and maximize vision; however, this study demonstrates that further gains in visual acuity can be achieved even after patients have received 24 months of treatment for DME. ■

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