SAVE (Super-dose Anti-VEGF) Trial: 2.0 mg Ranibizumab for Recalcitrant Neovascular Age-Related Macular Degeneration: 1-Year Results

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OBJECTIVES: To assess durability of visual and anatomic gains with 2.0 mg ranibizumab in recalcitrant neovascular age-related macular degeneration (AMD).

METHODS: Phase I-II trial of 88 patients with recalcitrant neovascular AMD treated as needed every 4 (cohort A) or 6 weeks (cohort B) following three monthly doses. ETDRS refraction and spectral-domain OCT–guided as-needed re-treatments.

RESULTS: Seventy-nine patients completed the 12-month endpoint and were given 11.6 (cohort A) and 8.6 (cohort B) mean treatments. Mean best corrected visual acuity gains of 4.1 letters following three monthly doses were sustained for 12 months for both cohorts. Anatomic improvements were sustained for 12 months for cohort A, but not for cohort B; cohort B demonstrated a gradual increase in mean central retinal thickness ($P = .03$).

CONCLUSION: Visual and anatomic gains achieved with 2.0 mg ranibizumab in recalcitrant neovascular AMD were sustained for 1 year with monthly treatment. In comparison, anatomic gains were diminished with less than monthly treatment.


INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of vision loss.1 Most blindness associated with AMD is due to its neovascular form.2 Pharmaceutical agents that block vascular endothelial growth factor (VEGF) have revolutionized the management of neovascular AMD, and clinical blockade of VEGF by intravitreal injection of Lucentis (ranibizumab; Genentech, South San Francisco, CA),3,4 Avastin (bevacizumab; Genentech, South San Francisco, CA),5 or Eylea (aflibercept; Regeneron, Tarrytown, NJ)6 is remarkably effective.

Nevertheless, many patients prescribed fixed-interval dosing with anti-VEGF agents manifest recalcitrant fluid. For example, in the Comparison of Age-related Macular Degeneration Treatment Trial (CATT), despite monthly treatment with anti-VEGF agents for 1 year, 53.2% of patients treated with ranibizumab and 70.9% of patients given bevacizumab showed evidence of persistent fluid on time-domain optical coherence tomography (OCT).7

Evidence suggests that some of these patients may benefit from a higher dose of anti-VEGF medications, an effect that may be particularly important in eyes considered incomplete responders, defined as eyes showing persistent exudation despite monthly treatment. Delivery of a higher dose of a given medication can be achieved in two manners. More frequent dosing can markedly improve through drug binding activity while having minimal impact on peak binding activity; this theory has been successfully applied with dos-
ing every 2 weeks for patients with VEGF-dependent macular edema refractory to monthly dosing. Alternatively, a higher medication concentration can be delivered at the same frequency. The Superdose Anti-VEGF (SAVE) trial was designed to assess the efficacy and safety of 2.0 mg intravitreal injections of ranibizumab for the treatment of recalcitrant neovascular AMD, a fourfold higher dose than the U.S. Food and Drug Administration–approved dose of 0.5 mg. The results of the fixed dosing regimen (after three monthly doses) have recently been reported. At study entry, patients had received an average of 24 prior intravitreal injections of anti-VEGF agents, including a median of 11 injections within the year before enrollment, with an average time between injections of 31 days. Despite this aggressive anti-VEGF treatment prior to enrollment in SAVE, rapid clinical improvement was observed in SAVE patients after three monthly injections of 2.0 mg ranibizum-
and 20/320 (Snellen equivalent), and total area of subretinal hemorrhage and fibrosis comprising less than 50% of the total lesion. Persistent SD-OCT leakage was defined as any of the following: intraretinal cysts, subretinal fluid, and/or serous pigment epithelial detachment (PED). At baseline, patients were randomized 1:1 to cohort A or cohort B. At all visits, subjects underwent ETDRS-refracted BCVA testing at 4 meters, Goldmann applanation tonometry, slit lamp examination, dilated ophthalmic examination, and SD-OCT using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany).

All subjects received 0.05 mL intravitreal injections of 2.0 mg ranibizumab administered every 4 weeks for three injections, with the first injection at baseline. Patients were then evaluated every 4 weeks (cohort A) or every 6 weeks (cohort B) and treated according to a capped PRN protocol. PRN treatments were performed for any intraretinal cysts, subretinal fluid, or sub-RPE fluid seen on SD-OCT. All patients received a minimum of quarterly treatment (months 5, 8, and 11) after the first three monthly injections during the PRN phase. Six-month and 12-month endpoints were selected for each cohort as close to these intervals as possible. Therefore, 6- and 12-month endpoints were measured at 6 and 12 months for cohort A and 6.5 and 11 months for cohort B; this was 4 weeks after the last injection for cohort A and 6 weeks after the last injection for cohort B, as was indicated by their prescribed regimens.

Sterile surgical technique was followed for every injection. Patients self-administered topical antimicrobials four times daily for 3 days prior to treatment. After topical anesthesia, the periocular skin, eyelids, and eyelashes were disinfected with 10% povidone-iodine swabs and 5% povidone-iodine ophthalmic solution was applied to the ocular surface. Following intravitreal injection, finger-counting testing was performed to confirm central retinal artery perfusion.

The primary endpoint was the mean change in baseline ETDRS BCVA at month 12. Secondary endpoints included the percentage of patients who experienced a loss or gain of 15 or more letters from baseline, mean change in central retinal subfield thickness (CST) over time as assessed by image-tracked Heidelberg Spectralis volume scans (20° × 20°, 49 lines, 768 A-scans per line) with nine-times image averaging, and the incidence and severity of ocular and nonocular adverse events. All SD-OCT segmentations (internal limiting membrane and Bruch’s membrane) on the Heidelberg Spectralis were manually corrected prior to computation of change maps and change in central retinal thickness. Statistical comparisons were performed with Student’s t tests, paired Student’s t tests, chi-square, and McNemar’s test using Statistical Analysis Software 9.1.3 (SAS Institute, Cary, NC) where appropriate.

RESULTS

Eighty-eight patients were enrolled between January 2010 and January 2011. Baseline demographics and clinical findings were well balanced between cohort A (n = 46) and cohort B (n = 42) and have been reported. Three patients (one from cohort A and two from cohort B) withdrew from the trial within the first three monthly treatments and are excluded from this
analysis. Seventy-nine patients completed 1 year of the SAVE study (cohort A = 43, cohort B = 36). Six patients (two from cohort A and four from cohort B) completed the initial three monthly loading doses and withdrew at months 5 (n = 2), 6.5 (n = 1), 9 (n = 1), and 11 (n = 2) due to difficulties with transportation, death, and other medical conditions precluding study visits; corresponding data are included until the date of study participation withdrawal.

Of the 79 patients who completed 1 year, the mean number of treatments given were 11.6 (range: 7 to 12) and 8.6 (range: 6 to 9) for cohorts A and B of a maximum of 12 and nine possible injections, respectively. A majority of patients, 32 (74%) and 23 (64%) of cohort A and B, respectively, received all possible PRN injections.

Mean ETDRS BCVA gains were similar between cohorts, improving significantly during the three monthly treatments and subsequently remaining stable through month 12. At month 2, BCVA improved by 4.5 and 3.5 letters for cohorts A (n = 45) and B (n = 40, respectively (P = 0.4). At month 6, BCVA gains remained stable at 4.4 and 3.8 letters for cohorts A (n = 42) and B (n = 36), respectively (P = .2). At month 12, BCVA gain was identical between the groups, 4.1 for cohort A (n = 43) and 4.1 for cohort B (n = 36) (Figure 1). At month 12, five (12%) and three (8%) patients gained 15 or more ETDRS letters in cohorts A and B, respectively. At month 12, one patient (2%) in cohort A lost more than 15 ETDRS letters, losing 21 due to a subretinal hemorrhage.

Anatomic improvement by SD-OCT with reduced intraretinal and subretinal fluid was similar between cohorts with three monthly treatments. Mean SD-OCT CST improved –35.7 µm and –55.4 µm from baseline at month 2 for cohorts A and B, respectively. Mean SD-OCT CST for cohort A continued to decrease at month 6 (–45.3 µm) and month 12 (–59.2 µm). In comparison, mean SD-OCT CST for cohort B subsequently increased at month 6 (–35 µm) and month 12 (–31.8 µm) compared to month 2. This difference in the trend for retinal thinning versus retinal thickening for cohorts A and B, respectively, was statistically significant by a comparison of group means using a paired t test (t = –3.05, P = .03, Figure 2) and clinically evident (Figure 3). At month 12, 12 (n = 43; 28%) and eight (n = 36; 22%) patients from cohorts A and B, respectively, had no detectable intraretinal or subretinal fluid by SD-OCT. While on average there was minimal resolution of sub-RPE fluid, some large pigment epithelial detachments flattened significantly (Figure 4).

Ocular and systemic adverse events are reported in Table. There were no significant differences between cohorts. There were no cases of endophthalmitis, traumatic cataract, or intraocular inflammation. One of 79 patients (1%) from cohort B with a large retinal pigment epithelial (RPE) detachment developed a tear of the RPE at month 9.5. Two of 79 patients (3%), one from each cohort, experienced myocardial infarctions at months 5 and 7, and there was one death in 79 patients (1%) in cohort A at month 12 associated with pneumonia and kidney failure.

**DISCUSSION**

In this prospective trial of neovascular AMD patients with incomplete anatomic responses to conventional VEGF blockade, 2.0 mg ranibizumab was effective at improving BCVA. Visual gain was
achieved during the first three monthly treatments and then sustained over 12 months with either 4-week or 6-week follow-up intervals with a capped PRN treatment protocol. Highlighting the recalcitrant nature of the choroidal neovascular complexes in these patients, the majority of patients required treatment at every PRN visit due to the presence of exudative disease activity. Both cohorts gained a mean of 4.1 ETDRS letters at month 12 compared to baseline, after having received a mean of 11.6 (cohort A) and 8.6 (cohort B) injections; therefore, similar visual gains were maintained with 26% fewer injections in the every-6-weeks follow-up arm.

A different trend was observed anatomically. Both cohorts demonstrated rapid central retinal thinning with three initial monthly doses. With continued monthly treatment, mean central retinal thickness subsequently continued to decrease through 1 year for cohort A. In comparison, a portion of the initial anatomic improvement observed following three monthly doses was slowly lost over the ensuing 10 months for cohort B, with a gradual increase in mean central retinal thickness that was statistically significant ($P = .03$) and clinically evident in some patients.

If ranibizumab exhibited linear pharmokinetics in the vitreous, a fourfold higher dose would be expected to extend biologic efficacy. The reduced anatomic effectiveness in cohort B (with less than monthly examination and PRN treatment) implies that 2.0 mg ranibizumab dosing does not extend the treatment interval beyond monthly therapy in patients with recalcitrant neovascular AMD with respect to retinal deturgescence. Possible explanations for this include loss of efficacy of the drug with extended exposure to physiologic conditions in the vitreous milieu, an increased vitreous clearance of drug in these recalcitrant eyes, or nonlinear pharmacokinetic elimination of ranibizumab.

The correlation between visual and anatomic outcomes can be distinct. For example, in the VIEW1 and 2 trials involving treatment-naive neovascular AMD patients, visual acuity outcomes were excellent and equivalent among all three arms: ranibizumab 0.5 mg monthly, aflibercept 2.0 mg monthly, and aflibercept 2.0 mg every other month after three initial monthly treatments. However, anatomic analysis revealed a different pattern. Central macular thickness (CMT) as measured by time-domain OCT in the 2-mg arm treated every 2 months revealed a “sawtooth-pattern” after the initial three monthly loading doses; CMT transiently increased at the end of the 2-month inter-

Figure 4. Case example of progressive reduction of serous pigment epithelial detachment with monthly ranibizumab treatment (cohort A): baseline infrared image (A) with marked SD-OCT location with sequential SD-OCT images at baseline (B), 3 months (C), 6 months (D), 9 months (E), and 12 months (F).
val and then decreased upon re-treatment. If we presume macular thickening in the setting of wet AMD is VEGF-dependent, this finding suggested incomplete blockade 2 months after treatment in at least a subset of the population. Despite this anatomic effect of apparent VEGF activity, there was no evidence that this affected visual outcomes at 12 months. A similar anatomic phenomenon was observed in CLEAR-IT 2, a phase II study of aflibercept. Despite our hope that objective OCT anatomic imaging can be used as a surrogate for visual acuity or visual response to treatment, evidence suggests the relationship is complex.

The clinical benefits of higher doses of anti-VEGF medications have been investigated in other trials involving patients with wet AMD. The phase III HARBOR study recently reported no difference in visual or anatomic outcomes in treatment-naïve patients randomized to 2.0 mg ranibizumab compared to 0.5 mg ranibizumab at the 1-year endpoint. In contrast to SAVE, HARBOR included only treatment-naïve eyes. Supporting the idea that a higher dose of anti-VEGF medication may be more valuable in neovascular AMD patients with incomplete anatomic response to conventional therapy, Fung et al reported a group of seven recalcitrant wet AMD patients treated with 2.0 mg ranibizumab who experienced visual gain and anatomic improvement. Similarly, an extended-release device, which maintains therapeutic vitreous concentrations of ranibizumab, or other anti-VEGF agents may be particularly valuable in this population of patients who require chronic, intensive therapy.

The safety of 2.0 mg intravitreal dosing was consistent with previous trials of ranibizumab, with no ocular or systemic safety concerns.

In summary, the 12-month endpoint of SAVE revealed that 2.0 mg ranibizumab may be valuable in the management of eyes with recalcitrant neovascular AMD.

REFERENCES