Early and Long-Term Responses to Anti–Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema: Analysis of Protocol I Data

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• PURPOSE: To determine whether early visual acuity response to ranibizumab in diabetic macular edema is associated with long-term outcome.
• DESIGN: Post hoc analysis of randomized controlled trial data.
• METHODS: Pooled data from the ranibizumab plus prompt and deferred laser treatment arms of the Diabetic Retinopathy Clinical Research Network’s Protocol I study were used to explore the relationship between early (week 12) and late (weeks 52–156) visual acuity response (mean change from baseline in best-corrected visual acuity [CFB BCVA]; categorized improvement [<5, 5–9, or ≥10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] in BCVA).
• RESULTS: In the analysis population (340 eyes), <5-, 5- to 9-, and ≥10-letter BCVA improvements occurred in 39.7%, 23.2%, and 37.1% of eyes, respectively, at 12 weeks, and 34.2%, 16.5%, and 49.3% of eyes at 156 weeks. Within each early BCVA response category (<5, 5–9, and ≥10 letters of improvement at 12 weeks), mean CFB BCVA at 52–156 weeks varied by <5 letters from that at 12 weeks. CFB BCVA and <5-letter improvement at 12 weeks showed significant positive and negative association, respectively, with CFB BCVA and ≥10-letter improvement at 52 and 156 weeks. Similar relationships were demonstrated in eyes with baseline BCVA <69 letters, and associations remained significant after multivariate adjustment for potential confounders.

• CONCLUSIONS: Ranibizumab ± laser therapy resulted in similar rates (~40%) of suboptimal (<5-letter) and pronounced (≥10-letter) BCVA improvement at 12 weeks. Eyes with suboptimal early BCVA response showed poorer long-term visual outcomes than eyes with pronounced early response (mean improvement 3.0 vs 13.8 letters at 156 weeks). (Am J Ophthalmol 2016;172:72–79. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

MULTIPLE RANDOMIZED CLINICAL TRIALS INDICATE THAT INTRAVITREAL ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) THERAPY, USED ALONE OR IN CONJUNCTION WITH FOCAL/GRID LASER PHOTOCOAGULATION, IS MORE EFFECTIVE THAN LASER PHOTOCOAGULATION ALONE IN IMPROVING VISUAL ACUITY IN DIABETIC MACULAR EDEMA (DME), WITH ~30%–70% OF PATIENTS ACHIEVING ≥10-LETTER IMPROVEMENT AND ~10%–40% OF PATIENTS ACHIEVING ≥15-LETTER IMPROVEMENT IN BEST-CORRECTED VISUAL ACUITY (BCVA) AFTER 1 YEAR OF TREATMENT.1–6 However, even with the intensive treatment schedules (monthly or near-monthly intravitreal injections for the first 12 months) and close patient monitoring typically employed in controlled clinical trials, more than 35% of patients with DME fail to achieve ≥10-letter improvement in BCVA and more than 55% fail to achieve ≥15-letter improvement after 2 years of first-line anti-VEGF therapy.3–6 Although anti-VEGF therapy is generally considered suitable first-line therapy for center-involved DME, clearly not all DME patients respond satisfactorily to anti-VEGF agents. Early identification of those patients who are likely to prove unresponsive or only partly responsive to long-term anti-VEGF therapy would enable more timely consideration of potential changes to their treatment regimens that might prove more effective in improving visual function and/or preventing vision loss. To this end, the EARLY (Early Anti-VEGF Response and Long-term efficacyY) program, a series of post hoc analyses of data from the Diabetic Retinopathy Clinical Research Network’s (DRCR.net) Protocol I study of ranibizumab plus laser in DME,3 was initiated to explore the relationship between early and...
long-term anatomic and visual acuity responses to anti-VEGF therapy. The present analysis assesses the strength of the association between visual acuity outcome after 12 weeks of anti-VEGF therapy (ie, after 3 monthly intravitreal injections) and visual acuity outcomes at 1 and 3 years.

METHODS

• STUDY OVERVIEW: In Protocol I (clinicaltrials.gov identifier NCT00445003), a large, prospective, multicenter trial in DME patients with baseline BCVA of 78-24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (approximate Snellen equivalent 20/32 to 20/320) and optical coherence tomography (OCT)-determined central subfield retinal thickness (CRT) ≥250 μm, study eyes were randomized to 1 of 4 treatment arms: (1) sham injection plus prompt (within 7–10 days) focal/grid photocoagulation, (2) intravitreal ranibizumab 0.5 mg plus prompt (within 7–10 days) focal/grid photocoagulation, (3) intravitreal ranibizumab 0.5 mg plus deferred (after ≥24 weeks) focal/grid photocoagulation, or (4) intravitreal triamcinolone 4 mg plus prompt (within 7–10 days) focal/grid photocoagulation. Intravitreal ranibizumab and sham injections were performed every 4 weeks for the first 12 weeks of the study and as needed thereafter; laser retreatment was determined by the extent of central macular edema. Eyes that met prespecified “failure” or “futility” criteria or were withdrawn from study treatment were included in the analysis. Follow-up examinations, including measurements of BCVA and OCT-derived CRT, were performed every 4 weeks for the first year and every 4–16 weeks during the second and third years of the study. Follow-up was planned for 3 years, with the primary outcome being at 1 year. After review of study findings at 2 years, which demonstrated an efficacy advantage in the ranibizumab treatment arms, patients in the sham injection and intravitreal triamcinolone treatment arms were offered the option of switching to ranibizumab treatment for the third year. The study follow-up period was subsequently extended to 5 years.

• VISUAL ACUITY RESPONSE ANALYSES: The present analysis is based on 3-year study data from those patients in Protocol I who were randomized to treatment with ranibizumab plus either prompt or deferred laser, and who provided an observed BCVA reading at 12 weeks. To evaluate the strength of the association between early treatment response and long-term outcome, study eyes were separately categorized according to the change from baseline in BCVA (<5-letter, 5- to 9-letter, or ≥10-letter improvement) at 12 weeks. Visual acuity outcomes at subsequent follow-up visits were determined with study cohorts based on these initial BCVA response categories. Missing data owing to missed visits after week 12 were imputed using the last-observation-carried-forward method. BCVA readings obtained after introduction of alternative treatments to the randomly assigned study treatment were included in the analysis. In view of the possibility that the improvement in BCVA might be truncated by a ceiling effect among eyes initiating treatment with good visual acuity, a sensitivity analysis was performed in the subset of eyes with baseline BCVA <69 ETDRS letters (Snellen equivalent ~20/50). Additional sensitivity analyses were performed in study eyes randomized to treatment with intravitreal ranibizumab plus deferred laser and in eyes categorized according to early BCVA response at other time points, ranging from 4 to 24 weeks after treatment initiation.

• STATISTICAL METHODS: Intercohort comparisons of baseline characteristics were performed using the Student t test for continuous variables and Pearson χ² test for categorical variables. Intercohort comparisons of vision outcomes (change from baseline in BCVA) were performed using analysis of variance. Multiple linear and logistic regression analysis was performed to assess the relationship between early (12-week) and late (52- and 156-week) visual acuity outcomes after controlling for multiple potential confounding factors. Additional covariates of interest included age, sex, baseline BCVA and CRT, proportional CRT response (≥20% vs <20% reduction from baseline) at 12 weeks, cumulative number of ranibizumab injections and laser treatments received at 52 and 156 weeks, and prior receipt of DME treatment. P values were determined using Student t test (linear regression) and Wald’s χ² test (logistic regression). Statistical analyses were performed with SAS versions 9.3 and 9.4 (SAS Inc, Cary, North Carolina, USA). A P value of ≤.05 was considered statistically significant.

RESULTS

IN TOTAL, 375 STUDY EYES WERE ASSIGNED TO THE ranibizumab plus prompt laser and ranibizumab plus deferred laser treatment arms in the Protocol I study. Of these, 340 study eyes provided observed visual acuity data and 335 study eyes provided observed OCT-derived CRT data at 12 (± 2) weeks (pooled analysis population). Within this overall population, sensitivity analyses were conducted on 212 eyes that had baseline BCVA <69 ETDRS letters.

• VISUAL ACUITY OUTCOMES: Overall best-corrected visual acuity response rate over time. Among the pooled analysis population (n = 340), 135 eyes (39.7%) showed <5-letter improvement in BCVA at 12 weeks, 79 eyes (23.2%)
showed 5- to 9-letter improvement, and 126 eyes (37.1%) showed ≥10-letter improvement; within this latter category, 60 eyes (17.6% of total) achieved ≥15-letter improvement. Overall, at study end (156 weeks), 116 eyes (34.2%) showed <5-letter improvement, 56 eyes (16.5%) showed 5- to 9-letter improvement, and 167 eyes (49.3%) showed ≥10-letter improvement from baseline; of this latter group, 98 eyes (28.9% of total) achieved ≥15-letter improvement.

Relationship between best-corrected visual acuity responses at 12 weeks and 1 and 3 years. Within each of the initial BCVA response categories (ie, BCVA improvement <5 letters, 5–9 letters, and ≥10 letters at 12 weeks), the mean BCVA response (BCVA change from baseline) of study eyes at 52 weeks onward did not vary by more than 5 ETDRS letters from the observed mean BCVA response at 12 weeks (Figure 1). Across the 3 response categories, intercohort differences in mean BCVA response (BCVA change from baseline) were statistically significant (P < .001) at each 4-week time point. Marked intersubject variation in BCVA response was evident within each initial response category, and a limited initial BCVA response (BCVA change from baseline) did not entirely preclude later development of a pronounced BCVA response during long-term treatment. However, development of the response was slow.

Within the subset of eyes with <5-letter BCVA improvement at 12 weeks, a minority of eyes achieved a BCVA gain of ≥10 ETDRS letters over the course of the study: 23.0% at 52 weeks, rising marginally to 28.9% at 156 weeks (Figure 2). A smaller minority of eyes achieved a BCVA gain of ≥15 ETDRS letters: 6.7% at 52 weeks, increasing to 14.8% at 156 weeks. Approximately one-half of eyes continued to show <5-letter BCVA improvement at these time points. Within the subset of eyes with a pronounced initial BCVA response (≥10-letter improvement at 12 weeks), most eyes maintained this response over the course of the study: 81.7% at 52 weeks and 72.0% at 156 weeks, and approximately one-half of eyes showed ≥15-letter improvement at these time points (61.1% and 47.2% of eyes, respectively) (Figure 3). A small proportion of eyes with ≥10-letter BCVA improvement at 12 weeks experienced subsequent attenuation of response to <5-letter improvement at 52 and 156 weeks.

Intercohort comparisons revealed significant differences in the baseline characteristics of study eyes: eyes with <5-letter improvement in BCVA at 12 weeks were older and had a higher baseline BCVA and a lower baseline CRT than eyes with ≥10-letter improvement in BCVA at 12 weeks (Table 1). In multiple logistic regression analyses there was a negative, statistically significant association between limited BCVA response (<5-letter improvement in BCVA from baseline) at 12 weeks and pronounced BCVA response (≥10-letter improvement in BCVA from baseline) at 12 weeks, and pronounced BCVA response (≥10-letter improvement in BCVA from baseline) at 12 weeks and pronounced BCVA response (≥10-letter improvement in BCVA from baseline) at 52 weeks and 156 weeks. Additionally, in multiple linear

FIGURE 1. Mean (95% confidence interval) change from baseline (BL) in best-corrected visual acuity (BCVA) over time, categorized by BCVA response at 12 weeks, in pooled study eyes treated with ranibizumab + prompt/deferred laser (n = 340 eyes). P value for comparison across all 3 BCVA categories (for each visit) is based on analysis of variance.
regression analyses BCVA response (BCVA change from baseline) at 12 weeks showed a significant association with BCVA response (BCVA change from baseline) at 52 weeks (coefficient estimate 0.72, standard error [SE] 0.07; \( P < .001 \)) and 156 weeks (coefficient estimate 0.56, SE 0.10; \( P < .001 \)) after adjusting for the standard covariates listed above. Age and baseline BCVA also showed significant associations with BCVA response (change from baseline) at 52 weeks, although only baseline BCVA remained significantly associated with BCVA response at study end (Table 3).

**SENSITIVITY ANALYSES:** Eyes with baseline best-corrected visual acuity < 69 ETDRS letters. Among the subset of eyes with baseline BCVA < 69 ETDRS letters (\( n = 212 \)), the distribution of early BCVA responses was marginally more favorable than in the overall study population, with <5-, 5- to 9-, and ≥10-letter BCVA improvements occurring in 32.1%, 21.2%, and 46.7% of eyes, respectively, at 12 weeks. Of the eyes with baseline BCVA < 69 ETDRS letters and <5-letter improvement at 12 weeks, a minority of eyes achieved a BCVA gain of ≥10 letters over the course of the study (35.3% at both 24 and 52 weeks).

**FIGURE 2.** Long-term best-corrected visual acuity (BCVA) outcomes in the subgroup of ranibizumab + prompt/deferred laser–treated eyes with <5-letter improvement in BCVA at 12 weeks: frequency distribution of BCVA improvement (\( n = 135 \) eyes).

**FIGURE 3.** Long-term best-corrected visual acuity (BCVA) outcomes in the subgroup of ranibizumab + prompt/deferred laser–treated eyes with ≥10-letter improvement in BCVA at 12 weeks: frequency distribution of BCVA improvement (\( n = 126 \) eyes).
findings in the subset of eyes with baseline BCVA <52 and 156 weeks. Multiple logistic and linear regression findings in the subset of eyes with baseline BCVA <69 ETDRS letters were generally consistent with those in the overall analysis population. There was a negative, statistically significant association between limited BCVA response (<5-letter improvement in BCVA from baseline) at 12 weeks and pronounced BCVA response (≥10-letter improvement) at 52 weeks (OR 0.23, 95% CI 0.11–0.47; \( P < .001 \)) and 156 weeks (OR 0.24, 95% CI 0.12–0.48; \( P < .001 \)), after adjusting for the standard covariates used in the main analysis. Likewise, BCVA response (change in BCVA from baseline) at 12 weeks was strongly associated with BCVA response at 52 weeks (coefficient estimate 0.77, SE 0.09; \( P < .001 \)) and 156 weeks (coefficient estimate 0.63, SE 0.13; \( P < .001 \)), after adjusting for the standard covariates.

<table>
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<tr>
<th>Parameter</th>
<th>&lt;5-Letter Improvement</th>
<th>5- to 9-Letter Improvement</th>
<th>≥10-Letter Improvement</th>
<th>( P ) Value*</th>
</tr>
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<tr>
<td>Age, mean ± SD (y)</td>
<td>64.3 ± 9.3</td>
<td>61.9 ± 9.9</td>
<td>61.7 ± 10.1</td>
<td>.036</td>
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<td>Male sex, n (%)</td>
<td>78 (57.8)</td>
<td>38 (48.1)</td>
<td>75 (59.5)</td>
<td>.775</td>
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<td>Baseline BCVA, mean ± SD (letters)</td>
<td>65.2 ± 12.2</td>
<td>64.9 ± 9.8</td>
<td>58.5 ± 11.4</td>
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<td>Baseline CRT, mean ± SD (µm)</td>
<td>379 ± 112</td>
<td>384 ± 107</td>
<td>438 ± 136</td>
<td>&lt;.001</td>
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<td>Prior DME treatment, n (%)</td>
<td>86 (63.7)</td>
<td>49 (62.0)</td>
<td>74 (58.7)</td>
<td>.410</td>
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</tbody>
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**TABLE 1.** Baseline Characteristics of Pooled Study Eyes Treated With Ranibizumab + Prompt/Deferred Laser, Categorized by Best-Corrected Visual Acuity Response at 12 Weeks (N = 340)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>52 Weeks</th>
<th>156 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio</td>
<td>( P ) Value*</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Age</td>
<td>0.96</td>
<td>.007</td>
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<tr>
<td>Sex (F/M)</td>
<td>1.08</td>
<td>.768</td>
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<tr>
<td>Baseline BCVA</td>
<td>0.93</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline CRT</td>
<td>1.00</td>
<td>.202</td>
</tr>
<tr>
<td>BCVA CFB &lt;5 letters at week 12</td>
<td>0.20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥20% CRT improvement at week 12</td>
<td>1.80</td>
<td>.074</td>
</tr>
<tr>
<td>Cumulative no. RAN injections at week 52 or 156</td>
<td>0.94</td>
<td>.256</td>
</tr>
<tr>
<td>Cumulative no. laser treatments at week 52 or 156</td>
<td>0.85</td>
<td>.167</td>
</tr>
<tr>
<td>Prior DME treatment</td>
<td>0.64</td>
<td>.113</td>
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</tbody>
</table>

**TABLE 2.** Multiple Logistic Regression Analysis of ≥10-Letter Improvement in Best-Corrected Visual Acuity at 52 and 156 Weeks: Pooled Study Eyes Treated With Ranibizumab + Prompt/Deferred Laser (N = 335)

**TABLE 3.** Multiple Linear Regression Analysis of Change From Baseline in Best-Corrected Visual Acuity at 52 and 156 Weeks: Pooled Study Eyes Treated With Ranibizumab + Prompt/Deferred Laser (N = 335)

BCVA = best-corrected visual acuity; CFB = change from baseline; CRT = central retinal thickness; DME = diabetic macular edema; RAN = ranibizumab.

*P value based on Student’s t test.
Other sensitivity analyses. As in the pooled analysis population, multiple logistic and linear regression analyses in the subset of eyes randomized to treatment with ranibizumab plus deferred laser demonstrated significant associations between early and late BCVA outcomes. In separate multiple linear regression analysis models, early BCVA response (BCVA change from baseline) at each of the examined time points (4, 8, 12, 16, and 24 weeks) was found to show a significant association with long-term BCVA response (BCVA change from baseline at 52, 104, and 156 weeks), after controlling for the standard covariates listed above (P < .001 for early BCVA response parameter in all models).

**DISCUSSION**

**EVIDENCE FROM RANDOMIZED CLINICAL TRIALS OF ANTI-VEGF THERAPY IN DME** suggests that the improvement in visual acuity largely develops within the first 3–6 months of treatment, with further, more modest gains occurring over the longer term.3,8,9 In contrast, the anatomic response appears to develop more gradually, and the reduction in CRT may not level off until later in the course of treatment. 2,12

Our post hoc analysis of data from the DRCR.net Protocol I study indicates, firstly, that visual acuity outcomes vary considerably in DME patients receiving ranibizumab plus prompt or deferred laser treatment. After 3 months of treatment, ~40% of eyes show substantial improvement in BCVA (>10 letters), whereas a similar proportion show at best only limited BCVA gain (<5 letters). Long-term treatment produces only modest additional improvement in these figures, with ~50% of eyes achieving ≥10-letter gain and one third of eyes <5-letter gain after 3 years. Secondly, the functional responses to ranibizumab that are evident 12 weeks after treatment initiation are consistently and robustly associated with subsequent responses over the entire 3-year duration of treatment. Because baseline BCVA is also an important determinant of treatment response (the greatest letter gains occur in eyes with worse baseline vision), it is possible that the association between early and late BCVA response might be attributable to a ceiling effect—namely, the limited scope for further letter gain in the ~40% of study eyes with relatively well-preserved baseline vision (BCVA ≥69 ETDRS letters; Snellen equivalent ~20/50). This appears unlikely, however, as an equally strong association was evident in the subset of eyes with moderate vision loss (baseline BCVA <69 ETDRS letters); these eyes, in contrast, are under no such constraints in their ability to achieve large (≥15-letter) gains in visual acuity. In keeping with findings in the overall study eye population, early BCVA response also proved to be significantly associated with long-term visual acuity outcome in the subset of eyes treated with ranibizumab plus deferred laser. This latter scenario may more closely mirror clinical practice, where the tendency is to use laser as rescue therapy following intravitreal ranibizumab monotherapy, rather than as adjunctive therapy.13

It should be noted that a limited initial BCVA response does not entirely preclude the possibility of future development of a more complete BCVA response if treatment is continued. Approximately 30% of the eyes that showed <5-letter improvement in BCVA at 12 weeks (ie, ~12% of all study eyes) subsequently achieved a BCVA gain of ≥10 letters after 3 years of treatment, whereas ~50% continued with <5-letter improvement. The reason for this delayed improvement in visual acuity in some eyes but not in others is unclear: possible contributory factors might include differences in diabetic retinopathy severity, baseline BCVA, laser use, and intensity of pro re nata ranibizumab treatment and VEGF suppression during follow-up.14,15 In the absence of comparative data on the clinical characteristics and treatment patterns of patients in the different response categories, this analysis provides no prognostic clues that would assist in identifying likely long-term treatment responders among patients who show a limited early BCVA response to ranibizumab. Given these constraints, and the relatively low probability of further visual acuity improvement after a suboptimal initial response to ranibizumab with prompt or deferred laser therapy, it may be appropriate to consider adjustments to the treatment regimen for patients in this category. Potentially these might include use of adjunctive agents acting through non-VEGF–mediated pathways or replacement of ranibizumab—either with another anti-VEGF agent, laser, or a sustained-release corticosteroid. Little is currently known, however, about the effectiveness of non-VEGF–mediated treatments in eyes with limited response to previous anti-VEGF therapy. Neither the Protocol I study nor the current analysis addresses the question of whether patients with suboptimal response to ranibizumab with prompt or deferred laser treatment are likely to achieve better visual acuity outcomes with alternative therapies, or whether any specific treatment pathway offers a potential efficacy advantage. The subsequent treatment algorithm for patients with limited visual response to initial anti-VEGF therapy is, therefore, uncertain. The clinical importance of this topic has been recognized and is the subject of ongoing prospective clinical trials.

Consistent with findings from earlier investigations of factors influencing the visual acuity response to anti-VEGF therapy in DME,14,15 we found that OCT-defined anatomic response (≥20% CRT reduction) at 12 weeks showed an inconsistent and generally weak association with long-term visual acuity outcome. The absence of a consistent association between early anatomic and late visual outcomes is not unexpected, because retinal edema represents only 1 of several possible causes of reduced visual acuity.
It should be borne in mind that our findings are based on data generated from a rigorously conducted clinical trial in which patients were evaluated consistently every 4 weeks during the first year of treatment, with possible extension of visit intervals to every 8 or 16 weeks during the second and third years if predetermined treatment success criteria (BCVA Snellen equivalent 20/20 or better or OCT-derived CRT ≤250 μm) were satisfied. In clinical practice, DME patients typically make frequent outpatient visits, with most of these being for nonophthalmologic reasons, making it difficult to maintain intensive anti-VEGF treatment and monitoring over the long term. In a retrospective study of US claims data from the IMS LifeLink™ health plan database (Danbury, CT; 2010–2011 data), patients with newly diagnosed DME made on average 5.3 ophthalmologist visits during the first 12 months of anti-VEGF therapy (compared with an average of 12 visits in the Protocol I study) and received an average of 3.6 intravitreal injections per eye over this period (compared with a median of 9 injections per eye in the Protocol I study), and fewer than 6% of patients received 10 or more injections over the first 12 months. Our findings therefore represent a best-case scenario for DME patients. In real-world settings with lower rates of anti-VEGF injection, rates of suboptimal visual acuity response may be even greater. Genotypic and phenotypic factors may contribute to the suboptimal response to anti-VEGF therapy. Inter-individual variation in responsiveness to anti-VEGF therapy in DME may be attributable in part to polymorphism in the VEGF gene, and/or to differences in VEGF gene expression. The response to anti-VEGF therapy may be limited as a result of enhanced VEGF expression and/or redundancy of the VEGF target, thereby necessitating a more intensive dosing regimen or use of adjunctive treatments with alternative modes of action. Metabolic factors such as glucose regulation also appear to affect the visual and anatomic response to anti-VEGF therapy in eyes with DME, with tight glycemic control throughout the duration of anti-VEGF treatment leading to more robust improvements in BCVA and CRT. However, available evidence suggests that baseline biochemical indices such as serum hemoglobin A1c level show little correlation with subsequent response to anti-VEGF therapy. Limitations of this analysis include its post hoc nature. Additional factors that might potentially affect the success or failure of anti-VEGF therapy in DME, such as duration of DME, were not reported in the Protocol I study; therefore, these data were unavailable for inclusion in the analysis. Potential associations with other aspects of DME status (eg, presence of ischemia, severity of diabetic retinopathy), and level of glycemic control remain of interest for future analysis. Additionally, although this analysis assesses vision improvement, it does not determine whether the improvement results in attainment of near-normal levels of visual acuity or leaves patients with significant residual visual impairment. Likewise, the analysis does not establish the optimal time point for measuring early BCVA response. It should be noted, however, that in the linear regression models exploring the relationship between long-term BCVA response and BCVA/CRT response during the first 4–24 weeks of treatment, the regression coefficients associated with BCVA response at 16 weeks and 24 weeks were no greater than those associated with BCVA response at 12 weeks, which incidentally coincides with the end of the treatment initiation phase (receipt of the 3 initial monthly intraocular anti-VEGF injections) in clinical practice. These limitations notwithstanding, this study is the first to demonstrate the significance of early treatment response as a factor associated with long-term visual acuity outcome with anti-VEGF therapy in DME.

In conclusion, this analysis indicates that for those eyes that show limited initial visual improvement with anti-VEGF therapy, only a minority (~20%–30%) can be expected to develop a clinically significant visual response with continued intensive anti-VEGF treatment and monitoring over the following 1–3 years. Outside the randomized clinical trial setting, maintenance of the intensive treatment schedule and monitoring required to achieve these visual acuity gains presents a considerable challenge. Accordingly, for patients with a suboptimal visual response after the first 3 intravitreal anti-VEGF injections it may be appropriate to consider adjustments to the treatment regimen. Specific recommendations for subsequent medical management of patients with limited initial response to anti-VEGF therapy must, however, await the results of randomized clinical trials in this setting.

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REFERENCES


