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CLINICAL STUDY

Identification of time point to best define 'sub-optimal response' following intravitreal ranibizumab therapy for diabetic macular edema based on real-life data

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Abstract

Purpose **To determine the average time-point at which it is best to define 'sub-optimal response' after ranibizumab treatment for diabetic macular edema (DME) based on the data obtained from real-life clinical practice.**

Methods **In this retrospective observational study, 322 consecutive treatment naïve eyes with DME were treated with three loading doses of intravitreal ranibizumab followed by re-treatment based on decision of the treating physician on a case-by-case basis. The demographic data, clinic-based visual acuity measurements and central subfield thickness (CST) assessed on spectral domain optical coherence tomography (OCT) were evaluated at baseline (month 0), 1, 2, 3, 6, and 12 months.**

Results **On an average, the improvement in visual acuity and CST was first seen after the loading dose. However, the maximal response in terms of proportion of patients with improvement in visual acuity and/ or CST in this cohort was observed at 12 months. Patients who presented with low visual acuity at baseline (<37 ETDRS letters) were unlikely to attain driving vision with ranibizumab therapy.**

Conclusions **On an average, a 'sub-optimal response' after ranibizumab therapy is best defined at month 12 as patients may continue to improve with treatment.**

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Introduction

Diabetic macular edema (DME) is the most common cause of moderate visual impairment in patients with diabetic retinopathy and its prevalence varies from 0 to 3% in patients with recent diagnosis of diabetes increasing to 28% in patients with diabetes for more than 20 years.[1–3] Prospective, randomized clinical trials have shown that intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents are effective in reducing the macular thickness and improving the visual acuity in patients with DME.[4–11] However, despite strict clinical trial protocol driven treatment criteria, ~50% of patients treated with anti-VEGF agents for DME have 'persistent' or 'recurrent' edema on optical coherence tomography (OCT) at 12 months despite an improvement in visual acuity in the majority of cases.[12–14] Together, they represent 'sub-optimal response' to treatment.

Several definitions of 'persistent' or 'recurrent' DME exist. 'Persistent' DME may imply (i) a reduction of <10% of central subfield thickness (CST) from baseline or (ii) persistent excess CST above the normative data or above 300 μm on spectral domain OCT in clinical practice at 12 months.[14,15] Similarly, 'recurrent' DME is defined as (i) an increase by at least 10% from the achieved lowest CST or (ii) an increase above the normative values after achieving normative data at some point during the first 12 months.[4,14] The prevalence of 'persistent' or 'recurrent' DME (together termed 'sub-optimal response') as per the above definitions after 12-month anti-VEGF therapy in routine clinical practice, where re-treatment is not well-defined as in clinical trials, remains unclear.[16]

In addition, these definitions do not often take into account the visual acuity status. In fact,

change in visual acuity only modestly correlates with change in CST.[17] For patients, an improvement in visual acuity is surely more important than any structural alteration. Therefore, when we contemplate a switch or addition of therapy, our primary aim should be to ensure that the change in treatment could maximize the gain in visual acuity. As a result, it is important to define 'sub-optimal' response in terms of both visual acuity and macular thickness changes. Although sub-analysis of the Protocol I data, incorporating visual acuity and CST has been reported,[12,18] a similar analysis in a clinical setting is useful, providing new information about the number of patients showing 'sub-optimal' response in terms of both visual acuity and CST, because evaluating treatment decisions in daily practice is less stringent than in clinical trials.

In light of the above, the purpose of this study was to determine the categories of responders following intravitreal ranibizumab treatment for DME in real-life clinical practice to provide the average expected response in different categories of presenting VA and CST.

Materials and methods

In this retrospective study, records of consecutive treatment naive patients with DME, who received 0.5 mg intravitreal ranibizumab injections between January 2013 and December 2013 at Moorfields Eye Hospital Medical Retina Service, were reviewed. Inclusion criteria were: (i) presence of center-involving DME in the study eye at baseline; (ii) clinic-based visual acuity between 6/60 and 6/6; (iii) CST $>350\mu$m on OCT on Topcon OCT (equivalent to 400 μm on Spectralis OCT) and (iv) follow-up of at least 1 year after the first ranibizumab injection. Patients with history of vitrectomy, prior treatment with laser, uncontrolled glaucoma, uveitis and those lost to follow-up, were excluded from the study. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (ROAD reference number 14/047). Written informed consent was obtained from all patients.

We recorded demographic data, the clinic-based visual acuity in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, the CST on OCT (Topcon 3D-OCT 2000) and the injection record at every visit. The visits considered for this study included baseline (month 0), 1, 2, 3, 6, and 12 months. All patients underwent comprehensive eye examination, including visual acuity measurement, color fundus images, OCT and fundus fluorescein angiography (FFA) at baseline as per institutional DME protocol, thereafter only visual acuity measurement and OCT were performed, while FFA was repeated at the discretion of each physician.

The treatment protocol included three monthly intravitreal 0.5 mg ranibizumab injections as a loading phase and then PRN treatment, based on decision of the treating physician on a case-by-case basis. Re-treatment criteria included presence of macular fluid on SD-OCT and/or visual acuity change compared to the previous visit. If the decision was not to proceed with further treatment at a clinic visit, such patients were followed up at 4–8 weekly intervals and retreatment decisions were made at these visits. Focal laser and modified grid laser photocoagulation were performed as per standard ETDRS protocol at physician's discretion anytime after the first three ranibizumab injections. Patients requiring panretinal photocoagulation were also treated promptly during this period.

Statistical analysis

For the description of patients' characteristics at baseline, mean ± SD was used for continuous variables and counts with percentages for categorical variables. For the longitudinal comparisons of VA and CST between baseline and each time point, the Wilcoxon matched-pairs signed-ranks test was used; given that four comparisons were done, the level of statistical significance was set at $0.05/4 = 0.0125$, according to the Bonferroni correction.

Statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA). A P value < 0.05 was considered as statistically significant, apart from cases where the Bonferroni correction was adopted, as declared above.

Results

A total of 332 consecutive treatment naive eyes of 278 patients, who were initiated on ranibizumab treatment for DME and followed up for at least 12 months were evaluated for this study. The mean age of patients was 64.5 ± 11.3 years. 61.2% of patients ($n = 170$) were male and 38.8% ($n = 108$) female. Given that 54 patients (19.4%) had bilateral involvement, our analysis was eye-based. The number of eyes with available data regarding visual acuity and OCT at baseline was 332 (100%); at month 1, 323 (97.3%); at month 2, 324 (97.6%); at month 3, 314 (94.6%); at month 6, 318 (95.8%) and at month 12, 312 (93.8%). The mean number of injections given at month 12 was 6.7 ± 2.2. Ten (3%) patients had supplemental macular laser.

Response based on visual acuity

The mean visual acuity at baseline was 56.4 ± 15.3 ETDRS letters and significantly improved to 64.4 ± 15.0 ETDRS letters at month 12. Table 1 shows the proportion of

Table 1 Proportion of eyes with different visual acuity (ETDRS letters) score at baseline and month 1, 2, 3, 6 and 12

Visual acuity (ETDRS letters)	*0 (baseline)*	*Month 1*	*Month 2*	*Month 3*	*Month 6*	*Month 12*
>73	43 (13%)	57 (17.7%)	74 (22.8%)	79 (25.2%)	91 (28.6%)	108 (34.6%)
54–73	165 (49.7%)	179 (55.4%)	178 (54.9%)	159 (50.6%)	160 (50.3%)	144 (46.2%)
37–53	88 (26.5%)	59 (18.3%)	50 (15.4%)	56 (17.8%)	45 (14.2%)	32 (10.3%)
<37	36 (10.8%)	28 (8.7%)	22 (6.8%)	20 (6.4%)	22 (6.9%)	28 (9%)

Table 2 Proportion of eyes in various categories of visual acuity gain over time

Change in visual acuity from baseline	*Month 1*	*Month 2*	*Month 3*	*Month 6*	*Month 12*
≥10 letters gain	50 (15.5%)	74 (22.8%)	94 (29.9%)	101 (30.8%)	105 (33.7%)
5–9 letters gain	82 (25.4%)	110 (34.0%)	80 (25.5%)	82 (25.0%)	84 (26.9%)
<5 letters gain	96 (29.7%)	79 (24.4%)	67 (21.3%)	68 (21.4%)	63 (20.2%)

patients classified to various categories of visual acuity at different time-points in the whole cohort. A third of patients achieved driving vision in the treated eye (defined as better than 73 ETDRS letters) at 12 months and increased significantly compared to baseline (13 *vs* 34.6% for baseline and month 12, respectively, $P<0.01$). The proportion of patients achieving this outcome gradually increased at every visit. In addition, the proportion of eyes that met the criteria of moderate visual impairment (37–53 ETDRS letters) continued to decline at each visit from 26.5% at baseline to 10.3% at 12 months. Therefore, if visual acuity is utilized as the parameter to determine response to therapy, month 12 would be the best time-point to evaluate the effect of the therapy.

Table 2 shows the proportion of patients with change in visual acuity classified into various categories at different time points. The earliest response in terms of visual acuity gains is noted after the loading phase of the three monthly injections. However, in all categories of improvement in visual acuity, the proportion of patients with stable visual acuity (0–4 letters change) continued to decrease with a reciprocal increase in patients with improvement in visual acuity (≥5 letters) by month 12. A total of 174 eyes (55.4%) and 189 eyes (60.6%) gained >5 letters at month 3 and month 12, respectively, while 44 eyes (14.0%) and 62 eyes (19.9%) gained <15 letters at month 3 and month 12, respectively.

In order to assess the individual response to ranibizumab over time, we also categorized the response rates based on visual acuity gain and evaluated the course of response at month 6 and month 12, using the definitions of the sub-analysis of Protocol I data used in the EARLY study.[18] About 21% of eyes showed limited early response with gain in visual acuity of 0–4 ETDRS letters at month 3, while 10% of eyes in this category gained more than 10 letters at month 6 and 12. In addition, about 25% of patients had an intermediate early response of 5-9 ETDRS letters gain at month 3 and about 30% of patients showed strong early response after the 3 loading injections with ≥10 ETDRS letters gain, as it is shown on Table 2.

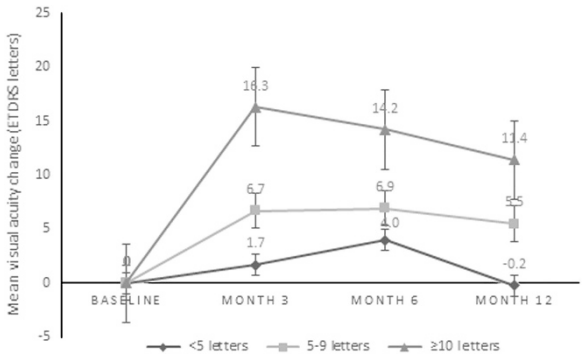

Figure 1 Graph showing the evolution of mean visual acuity change over time in patients with different response at month 3.

Figure 1 shows the mean change in visual acuity in the three groups of visual acuity gain. Patients, who showed early and strong response at month 3, were found to gain about 11.4 ETDRS letters at month 12, while patients with 'sub-optimal' response at month 3 presented about 0.2 ETDRS letters loss in mean visual acuity at month 12. However, it is worthy to note that in the category of 'sub-optimal' response (<5 ETDRS letters gain), about 25% of patients had visual acuity gain of more than 10 letters with current treatment at month 12, as it is shown on Table 3.

At an individual value, the ceiling effect was observed in patients who present with a visual acuity of more than 73 letters. Approximately 14% of patients in this category dropped to the less level of visual acuity (56–73 letters). In all other categories of visual acuity, most patients remained in the same category or improved.

Table 3 Proportion of patients with 'sub-optimal' response at month 3 and their evolution over time

3 months	*6 months* n *(%)*	*12 months* n *(%)*
<5 letters gain (21.3% of the study sample)	<5 letters gain 28/67 (41.8%) 5–9 letters gain 19/67 (28.4%) ≥10 letters gain 11/67 (16.4%)	<5 letters gain 18/67 (26.9%) 5–9 letters gain 18/67 (26.9%) ≥10 letters gain 16/67 (23.9%)

Table 4 Proportion of eyes with different central subfield thickness (CST) at baseline and month 1, 2, 3, 6 and 12

CST (μm)	*Baseline*	*Month 1*	*Month 2*	*Month 3*	*Month 6*	*Month 12*
≤300 μm	0 (0%)	86 (26.6%)	110 (34%)	134 (42.7%)	138 (43.4%)	146 (46.8%)
301-400 μm	107 (32.3%)	125 (38.7%)	133 (41.1%)	108 (34.4%)	102 (32.1%)	92 (29.5%)
401-500 μm	120 (36.1%)	77 (23.8%)	53 (16.4%)	46 (14.6%)	47 (14.8%)	42 (13.5%)
≥ 501 μm	105 (31.6%)	35 (10.8%)	28 (8.6%)	26 (8.3%)	31 (9.7%)	32 (10.3%)
Lowest CST value achieved	9 (2.7%)	16 (5.0%)	42 (13.0%)	77 (24.5%)	81 (25.5%)	107 (34.3%)
At least 10% decrease in CST from baseline		205 (65.3%)	247 (76.2)%	244 (78.7%)	239 (76.4%)	241 (78%)

None of the patients who present with visual acuity of less than 37 letters achieved more than 73 letters.

Response based on central subfield thickness

The mean CST was 468.4 ± 113.3 μm at baseline compared to 336.1 ± 123.4 μm at month 12 ($P<0.001$). Table 4 shows the proportion of eyes in different CST categories over time. The prevalence of persistent DME (CST > 300 μm) at month 12 was 53.4%. The proportion of eyes with CST ≤ 300 μm increased at every visit during the loading phase of 3 injections and then remained stable from month 3 to month 12. Moreover, the proportion of eyes with CST between 300 and 400 μm remained stable throughout the 12 months. On the contrary, the proportion of eyes with CST more than 400 μm decreased to a third by 12 months. It is worthy to note that 34.4% of eyes (the highest proportion) achieved the lowest CST value at month 12. When we consider the 26 (8.3%) patients with > 500 μm at month 3, 3 patients (11.5%) presented CST < 300 μm at month 6 and 4 patients (15.4%) at month 12.

It is worthy to note that in patients with visual acuity > 73 ETDRS letters, 51% of eyes presented CST > 300 μm at month 12, showing that persistent DME may exist despite the 'good' visual acuity. In addition, if one takes into account both visual acuity and CST, in this study, only 0.7 and 4.4% of eyes achieved a visual acuity of 6/6 and CST ≤ 300 μm at month 3 and month 12 respectively, suggesting that in real-life attainment visual acuity of 6/6 with resolution of fluid is a challenging task to achieve.

Discussion

The principal message of this study is that based on the definitions used to determine response to ranibizumab treatment for DME, the average time-point to consider 'sub-optimal' response to ranibizumab therapy is at month 12 as most patients continue to improve visual acuity over the 12 months' period. However, individual discretions may apply. For example, our data indicate that identifying 'sub-optimal' response after the loading phase may be more appropriate in patients with low visual acuity at baseline (<37 ETDRS letters).

Currently, there are no robust data to suggest that switch from one anti-VEGF therapy to another results in visual acuity gain and/or better resolution of macular fluid. On the basis of our experience in neovascular age related macular degeneration (AMD), a switch from ranibizumab to aflibercept resulted in anatomical improvement with resolution of macular fluid with no visual acuity gain.[19] However, given that the two diseases are different in pathophysiology, there are no exact data on switching between anti-VEGF agents in DME. In addition, Ferris *et al*[20] reported that due to the 'regression to the mean' phenomenon, it is difficult to assess the impact of switch from one to another anti-VEGF without a control group, and found that patients with DME and AMD presented increase in visual acuity even if they continued the same treatment and did not switch therapy by analyzing a subgroup of CATT and DRCR.net study. This study provides evidence of the same in real-life, in patients continuing on ranibizumab for 12 months despite <5 letters gain at month 3, since ~30% of them gained ≥5 letters subsequently in this cohort. Therefore, in a clinical trial, as switch to another agent should provide a superior response to this to prove the beneficial effect of the second agent.

The study also shows that the increase in visual acuity in patients with DME is a gradual process and the peak in visual acuity may be established only after 6–9 months or longer following initiation of treatment.[21] Very few

patients show 'sub-optimal' response after three loading injections and therefore, in general, it is better to wait longer to identify the true 'sub-optimal' responders. There may be exceptions to the rule that one could decide on a case-by-case basis.

Furthermore, there are few clinical trials on the role of switching from anti-VEGF to steroid therapy or addition of steroid therapy to on-going anti-VEGF therapy in DME.[22] Both the OZLASE and OZDRY studies included patients with long-standing and persistent edema despite previous laser and/or anti-VEGF therapy.[23,24] These studies did not show any visual benefit despite resolution of fluid at the end of the follow-up, using intravitreal dexamethasone implant (Ozurdex, Irvine, CA, USA). However, there are other studies, showing that intravitreal dexamethasone implant and intravitreal fluocinolone acetonide (Iluvien, Alpharetta, GA, USA) are effective in improving visual acuity and reducing macular thickness in patients with DME refractory to previous anti-VEGF therapy.[25–27] Randomized controlled trials are needed to confirm or disprove that a switch to another therapy can improve visual acuity in patients who are defined as 'sub-optimal responders' to anti-VEGF therapy.

Another interesting finding of our study was that unlike clinical trials, in real-life clinical practice, treatment decisions seemed to be more conservative. In clinical practice, the less stringent re-treatment criteria may be attributed to multiple factors, including tendency of clinicians to under-treat, patients' reluctance to have continuous regimen of repeated injections or due to strain on services to provide prompt and timely treatment. Therefore, a change in the initial treatment or use of combined therapy is often contemplated despite lack of evidence.

Potential limitation of this study is its retrospective nature. Moreover, it should be mentioned that visual acuity assessment was clinic-based. However, this study has a relatively large sample size and provides real-life data of a tertiary retina center.

In conclusion, in most instances, month 12 is an ideal time-point for identifying 'sub-optimal' treatment response after ranibizumab therapy, although month 3 may be more appropriate in patients with low visual acuity at baseline (<37 ETDRS letters).

Summary

What was known before

- There is no general consensus about when to switch ranibizumab treatment for diabetic macular edema and who were 'non-responders' to treatment.

What this study adds

- A patient with 'sub-optimal response' after ranibizumab therapy for diabetic macular edema is best defined at month 12 as patients may continue to improve with treatment.

Conflict of interest

PH and SS have received travel grants, research grants and speaker fees and attended advisory board meetings of Bayer, Allergan and Novartis.

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