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Dose-response analysis of ranibizumab as-needed regimens for visual improvement in patients with diabetic macular edema using a modelling approach

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ABSTRACT

Background: Ranibizumab and aflibercept are anti-vascular endothelial growth factor therapies for diabetic macular edema (DME) but have only been directly compared in one study: the Protocol T study, a 24-month randomized controlled trial which compared the safety and efficacy of three anti-VEGF agents (ranibizumab 0.3 mg, aflibercept 2.0 mg and bevacizumab 1.25 mg). The ranibizumab dose used in Protocol T is not licensed for use outside of the US, where a higher ranibizumab dose of 0.5 mg is approved. Therefore, the relevance of the head-to-head Protocol T study findings to healthcare providers in Europe is limited. The purpose of this research was to predict the visual outcomes that may have been achieved in Protocol T with ranibizumab 0.5 mg.

Methods: A simplified dose-response model was constructed to describe the relationship between average monthly dose and one-year best corrected visual acuity (BCVA) change from baseline. A linear mixed effects model was evaluated and Bayesian Monte-Carlo Markov chains method was used to estimate the model parameters.

Results: If ranibizumab 0.5 mg PRN had been studied in Protocol T, it would have resulted in a BCVA gain of 14–15 early treatment diabetic retinopathy study (ETDRS) letters; 3–4 letters more than the actual BCVA gain reported with ranibizumab 0.3 mg PRN. In Protocol T patients with poor baseline BCVA (< 69 letters), a similar additional letter gain would have been achieved.

Conclusion: The relevance of the Protocol T study findings are limited due to the use of ranibizumab 0.3 mg PRN which, based on the modelling approach reported herein, resulted in sub-optimal visual gains.

1. Introduction

Diabetic macular edema (DME) is a severe, vision threatening form of diabetic retinopathy (DR). Of the estimated 285 million diabetic patients globally, 35% are thought to have DR and 7% DME [1]. DME is therefore a leading cause of visual loss [1]. Central to the pathogenesis of DME is an elevation in the level of vascular endothelial growth factor (VEGF) as a consequence of hyperglycemia [2]. While laser photocoagulation therapy has proven efficacious in stabilizing vision in DME, therapies which target VEGF have proven superior by not only stabilizing, but actually improving vision in these patients [3,4].

Several randomized controlled trials (RCTs) have assessed the efficacy of anti-VEGF agents under various treatment regimens in DME, with all reporting some degree of visual gain [3–7]. In those studies which tested ranibizumab 0.5 mg over 12 months, visual gains ranged from 6.1 ETDRS letters to 10.3 ETDRS letters [4,5]. Two similarly designed studies have examined the efficacy of aflibercept 2.0 mg in DME – the VIVID study (Europe, Japan and Australia) and the VISTA study (US only) [8]. At Week 100, patients had gained 11.4 and 11.5 ETDRS letters in VIVID and VISTA, respectively (with q4 treatment), although

Abbreviations: DME, Diabetic macular edema.; DR, Diabetic retinopathy; VEGF, Vascular endothelial growth factor; RCT, Randomized controlled trial; ETDRS, Early treatment diabetic retinopathy study; VA, Visual acuity; PRN, Pro re nata; BCVA, Best corrected visual acuity; LOCF, Last observation carried forward; AMD, Age-related macular degeneration

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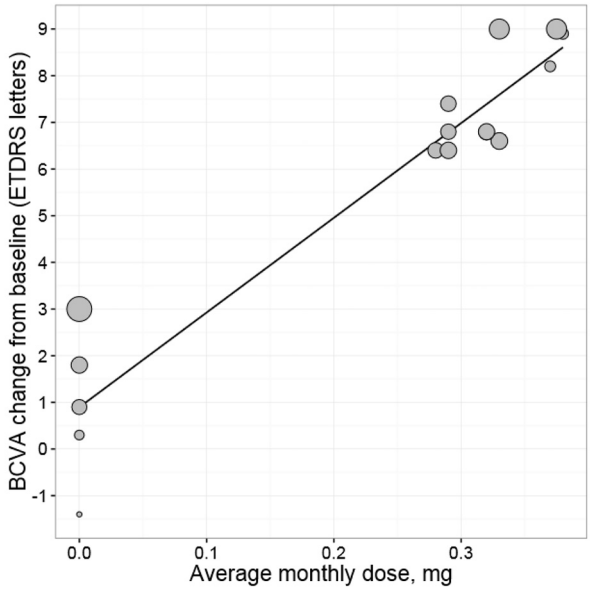


Legend:

Size of the dots is proportional to the size of the study arm

BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study

**Ranibizumab PRN data, excluding Protocol T*

Fig. 1. Observed change in BCVA from baseline versus average monthly ranibizumab dose (mg) over a one year period*, and regression line.

it should be noted that the baseline visual acuity (VA) was different between the aflibercept and ranibizumab studies due to differing inclusion criteria. This difference likely influenced the overall outcome as VA gain in response to treatment is known to be dependent on baseline VA. [9] Notably, however, there is only one study to date which has directly compared the treatment efficacy between ranibizumab and aflibercept in patients with DME – the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study [10].

The Protocol T study was a 12-month RCT which compared the safety and efficacy of three anti-VEGF agents in the treatment of DME: ranibizumab 0.3 mg, aflibercept 2.0 mg and bevacizumab 1.25 mg [10]. While ranibizumab 0.3 mg is approved by the Food & Drug Administration in the US, this dose is not licensed or widely studied outside of the US, where a higher dose of 0.5 mg pro re nata (PRN) is approved for use. Furthermore, the use of ranibizumab 0.3 mg in a PRN treatment regimen is not approved in the US. The 2-year results of the PROTOCOL T study showed similar visual outcomes for all 3 compared anti-VGEFs. The superiority of aflibercept over ranibizumab (0.3 mg) noted at the 1 year results was no longer identified [15].

Due to the approximately 40% lower dose of ranibizumab used, the relevance of the Protocol T study findings to healthcare providers outside of the US, i.e. Europe, Asia, Africa and beyond is limited.

The purpose of the current study is to address this limitation by developing a dose-response model for ranibizumab, and using it to predict the visual outcomes that may have been achieved if the outside-of-US licensed dose of ranibizumab (0.5 mg) had been used in the Protocol T study. This modelling approach was applied to the total study population, and to a subgroup of patients with poor baseline vision, in order to better understand the efficacy results reported in the Protocol T study outside of the US.

2. Methods

Exploratory data analysis identified six studies with patient-level data available in which DME patients not treated with a monthly regimen were extracted: RESOLVE [4], RESTORE [5], REVEAL [11], RESPOND [12], RETAIN [13], the DRCR.net Protocol I [14]. Patient-level data were extracted and used to plot mean change in best corrected visual acuity (BCVA) from baseline against average monthly anti-VEGF dose (Fig. 1 and Table 1), within a one-year period. Due to no access to more patient level data, no further clinical trials were included in the model development. Average monthly dose was calculated by dividing the average total amount of doses within one year by 12 (months). This plot revealed a seemingly linear relationship between these two variables, thus a linear model was used in the next stage – the formal dose-response modelling stage.

The dose-response model was constructed to describe the relationship between average monthly dose and one-year BCVA change from baseline, using summary data from seven studies (Table 1): RESOLVE [4], RESTORE [5], REVEAL [11], RESPOND [12], RETAIN [13], Protocol I [14], Protocol T [9]. This controlled for confounding factors associated with inter-study variability. As we wanted to describe the relationship in the context of individualized treatment regimens in which the investigators made the decision to treat or adjust the treatment interval, the RISE and RIDE studies (RBZ 0.5 or 0.3 mg) were not included in the model, In these studies ranibizumab were administered in a fixed, monthly dosing regimen.

For the average monthly dose (mg) and response in BCVA effect relationship, a linear mixed effects model was evaluated (Fig. 2). The model included a fixed (common) intercept and a random study specific

Table 1
Summary of study results and baseline characteristics.

Study	Comparator	Dose/month (mg)	n	BL BCVA	Δ BCVA	BL CRT	Age	% female	Number of injections
RESOLVE	Sham	0	49	61.1	−1.4	448.9	65	49	0
RESTORE	Laser	0	110	62.4	0.9	412.4	63.5	47.7	0
REVEAL	Laser	0	128	58.4	1.8	397	61.5	42.7	0
RESPOND	Laser	0	62	61.9	0.3	458	62.8	40.3	0
RESTORE	Laser + Rbz PRN	0.28	118	63.4	6.4	416.4	64	40.7	6.8
RESTORE	Rbz PRN	0.29	115	64.8	6.8	426.6	62.9	37.1	7
REVEAL	Laser + Rbz PRN	0.29	129	58.5	6.4	434.7	61.2	49.2	7
RETAIN	Rbz PRN	0.29	117	64.7	7.4	432.5	64.5	37.4	7
RETAIN	Laser + Rbz T&E	0.32	117	61.7	6.8	480.7	63.7	35.5	7.6
RETAIN	Rbz T&E	0.32	125	63.9	6.8	452.4	63	39.8	7.7
REVEAL	Rbz PRN	0.33	133	58.8	6.6	432.8	60.7	39.1	7.8
RESPOND	Laser + Rbz PRN	0.37	70	64.8	8.2	422.1	60.8	35.6	8.8
RESPOND	Rbz PRN	0.38	71	63.1	8.9	448.5	61.5	44	9.2
Protocol I	Sham + prompt laser	0	293	65	3.0	407	63	42	0
Protocol I	Rbz PRN + prompt laser	0.33	187	66	9.0	371	62	45	8
Protocol I	Rbz PRN + deferred laser	0.375	188	66	9.0	382	64	41	9

BCVA: best corrected visual acuity; BL: baseline; CRT: central retinal thickness; Rbz PRN: ranibizumab pro re nata; Rbz T&E: ranibizumab treat and extend.

$$\Delta BCVA_{ij} \sim N(\mu_{ij}, \sigma_1{}^2 / nij)$$

$$\mu_{ij} = a_0 + b_0 \cdot \exp(\gamma_i) \cdot Doseij \quad \gamma_i \sim N(0, \sigma_2{}^2),$$

Legend:

i=study; j=dose within study; nij=size of the study arm; a_0=the common interecept; b_0=average slope over the studies; γ_i=the study specific random effect of the slope; $\sigma_1{}^2$ and $\sigma_2{}^2$=the variance of the random effect of residuals and of the slope

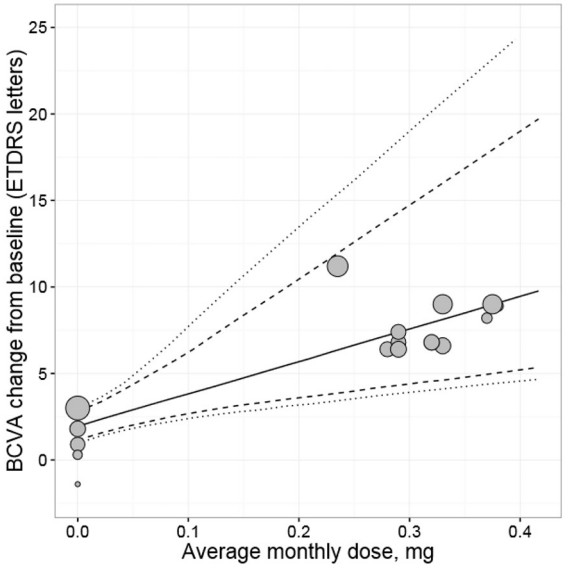
Fig. 2. Linear mixed effects model.

Table 2
Estimated parameter summaries.

Parameter	Mean	Standard deviation	Percentiles		
			25%	50%	75%
a_0	2.00	0.54	1.65	1.98	2.33
Log(b_0)	2.93	0.26	2.80	2.95	3.09
σ_2	0.51	0.25	0.34	0.45	0.60
σ_1	12.90	2.76	10.79	12.59	14.70

$$\Delta BCVA_{ij} \sim N(\mu_{ij}, \sigma_1{}^2 / nij)$$

$$\mu_{ij} = a_0 + b_0 \cdot \exp(\gamma_i) \cdot Doseij \quad \gamma_i \sim N(0, \sigma_2{}^2),$$



Legend:

BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study

Predicted VA response
90% prediction intervals
95% prediction intervals

Fig. 3. Linear mixed effect model showing predicted and observed BCVA change from baseline at one year.

slope. The intercept can be interpreted as the common placebo response across the studies. The size of the studies were taken into account in the model through the variance of the residuals.

Bayesian Monte-Carlo Markov chains method was used to estimate the model parameters. The Bayesian approach enables predictive simulations of new studies with model parameters sampled from joint posterior distribution of the parameters and thus fully accounting for the parameter uncertainties. A total of 1000 posterior samples of these parameters were generated (5000 burn in samples and thinning of every 100 samples). The result of this linear mixed effect model is listed in Table 2.

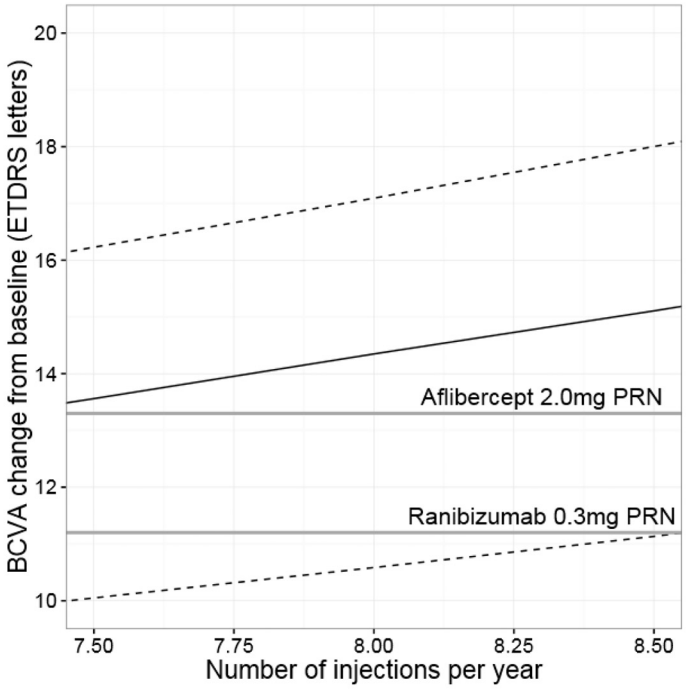
These 1000 simulated samples were used to predict BCVA change from baseline at Month 12 and average dose/month relationship. Only the treated patients for whom valid BCVA measurements for both baseline and actual one year visit (falling between Month 10 and Month 14) were selected for the analysis; no last observation carried forward (LOCF) imputation was made. The median profile of these 1000 Markov chain Monte-Carlo samples predicted profiles, along with its 90 and 95% predictive intervals, are displayed in Fig. 3. For the prediction of the functional response to ranibizumab 0.5 mg PRN in Protocol T, the 1000 samples of slope of Protocol T along with the common intercept were used. The median and the 95% prediction interval are illustrated in Fig. 4. The same model and method was applied on the subgroup of patients with < 69 BCVA letters at baseline in order to estimate the effect of ranibizumab 0.5 mg in that sub-group (Fig. 5). Although other covariates known to influence the response, eg age and retinal thickness, were not included in the model, it was noted that corresponding baseline features in protocol T were similar to those of the studies used to build the model. Hence the dose-response behavior in protocol T is deemed similar to the one estimated from the model.

3. Results

Mean change in BCVA from baseline versus average monthly anti-VEGF dose over 12 months is presented in Fig. 1. This pooled exploratory analysis indicated a linear dose response for ranibizumab 0.5 mg PRN regimens. These data were incorporated into the dose-response model.

The dose-response model predicted that if ranibizumab 0.5 mg PRN had been studied in Protocol T, it would have resulted in a BCVA gain of 14–15 ETDRS letters (Fig. 4). This prediction is 3–4 letters more than the actual BCVA gain reported with ranibizumab 0.3 mg PRN in Protocol T. Based on individual data from the ranibizumab studies listed previously, the mean (± SD) number of injections was 7.95 (± 2.66) within a one-year period. If ranibizumab 0.5 mg PRN had been studied in Protocol T patients with poor baseline BCVA (< 69 letters), it would have resulted in a VA gain of 17–18 ETDRS letters (Fig. 5). This prediction is 3–4 letters more than the actual BCVA gain reported with ranibizumab 0.3 mg PRN in that study. In this group, the mean (± SD) number of injections received was 8.30 (± 2.57) within a one-year period.

To assure that the proposed linear mixed effect model with a study specific slope was adequate, a more complex model including an additional study specific intercept was evaluated. The prediction of ranibizumab 0.5 PRN efficicacy for Protocol T based on the more complex model was illustrated along with that of the previous linear mixed effects model; the differences between these two models were minimal (Fig. 6).



Legend:

** Range of mostly observed numbers of yearly injections for ranibizumab 0.5 mg PRN*

PRN: pro re nata; BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study

Predicted VA response
95% prediction interval

Fig. 4. Predicted efficacy of ranibizumab 0.5 mg PRN for Protocol T (all patients) over a one-year period.

4. Discussion

An ever-growing body of favorable efficacy data has meant that anti-VEGF therapy has become the de-facto standard of care in DME [3–8]. The Protocol T study was the most recent head-to-head comparison of anti-VEGF agents used in DME. Specifically, Protocol T compared the safety and efficacy of ranibizumab 0.3 mg, aflibercept 2.0 mg and bevacizumab 1.25 mg in DME and reported significant visual improvement with all three interventions [9]. The interpretation of these findings is limited, however, by the use of ranibizumab 0.3 mg – a dose which is only 60% of the ranibizumab 0.5 mg dose licensed for use outside of the US. Thus, the Protocol T data are of limited use to healthcare providers who use ranibizumab 0.5 mg, i.e. those outside of the US.

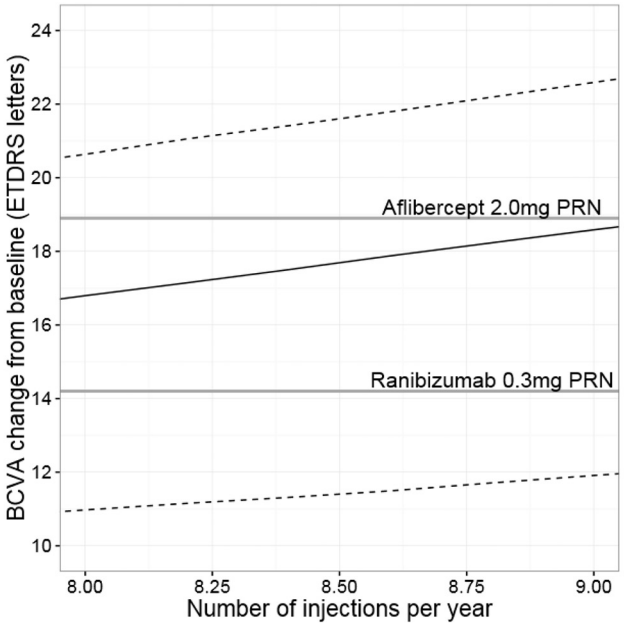
The model developed in the current study predicted that if ranibizumab 0.5 mg PRN had been studied in Protocol T, an additional 3–4 ETDRS letters may have been gained over that achieved with the lower dose of ranibizumab 0.3 mg. Furthermore, if ranibizumab 0.5 mg PRN had been studied in Protocol T patients with poor baseline vision (< 69 letters), these patients may also have gained 3–4 ETDRS letters more than that achieved with the lower dose of ranibizumab 0.3 mg. Our finding is noteworthy as it suggests that if the higher, approved dose of ranibizumab 0.5 mg had been used in the Protocol T study, the visual outcome in the ranibizumab group would have been greater.

The Protocol T study found that aflibercept 2.0 mg resulted in greater visual gains than ranibizumab 0.3 mg (and bevacizumab 1.25 mg) after 12 months in patients with baseline vision of < 69 letters. While it should be noted that this difference was no longer significant at 24 months [15], the finding at 12 months is not counter-intuitive in the context of the low ranibizumab dosage used. Indeed, it has been shown that vitreous VEGF levels are higher in DME patients [16] than in age-related macular degeneration (AMD) patients [17], and since ranibizumab 0.5 mg is the most effective dose in neovascular AMD, one would expect that 0.5 mg would also be the most effective dose in DME. In short, the lower dose of ranibizumab 0.3 mg may have resulted in sub-optimal treatment, and this assertion is supported by the findings from our model.

The findings of Protocol T are also inconsistent with previous studies. Looking at past studies of anti-VEGF therapy in DME, we see that visual gains tend to plateau at approximately 70 ETDRS letters at 12 months [9]. In Protocol T, however, anti-VEGF therapy achieved gains of 4–8 letters above this plateau.

Data comparing the efficacy of ranibizumab 0.3 mg versus ranibizumab 0.5 mg are limited, especially in DME. The Phase III RCTs RISE and RIDE compared these two ranibizumab doses versus sham injection in patients with DME [7]. At 36 months, the RIDE study reported that 40.2% of patients had gained > 15 letters with ranibizumab 0.5 mg, versus 36.8% of patients receiving ranibizumab 0.3 mg. In a pooled analysis of the RISE/RIDE data, VA gains in the ranibizumab 0.5 mg group were greater than gains in the ranibizumab 0.3 mg group in patients with poor vision at baseline. In the same analysis, it was found that a greater number of patients in the ranibizumab 0.3 mg arm required rescue laser treatment during the study [18].

The output from our model facilitates a greater understanding of the Protocol T findings. However, as with any model which includes data from multiple sources with the respective heterogenity, certain



Legend:

Number of injections per year = Range of mostly observed numbers of yearly injections for ranibizumab 0.5 mg PRN

PRN: pro re nata; BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study

Predicted VA response
95% prediction interval

Fig. 5. Predicted efficacy of ranibizumab 0.5 mg PRN for Protocol T patients with poor baseline vision (< 69 letters) over a one-year period.

limitations must be accepted. Primarily, it is not possible to control for all baseline variables across the studies included in the model. For example, baseline vision is known to be a key predictor of VA outcome after anti-VEGF therapy [9]. Input of trial data with varying mean baseline VAs into the model may influence the slope of the dose response curve, and consequentially, the overall efficacy prediction. These limitations confirm that modelling does not generate evidence of the same level as a randomized controlled trial. However, in the absence of head-to-head trials, modelling helps investigate the impact that lowering the dose of ranibuzumab might have on functional outcomes. The results suggest that a higher dose of ranibizumab might have been associated with improved visual outcome compared to the lower dose used in PROTOCOL T.

In conclusion, the relevance of the Protocol T study findings is questionable due to the use of ranibizumab 0.3 mg, a dosage which is not approved for use in DME outside of the US. The modelling approach reported herein suggests that the visual gain reported with ranibizumab 0.3 mg in the Protocol T study was sub-optimal. Our model predicts that ranibizumab 0.5 mg would have resulted in at least equivalent visual improvement versus aflibercept 2.0 mg had it been studied in Protocol T, and this may inform treatment choice in DME outside of the US.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Andreas Clemens, Etienne Pigoelet, Zufar Mulyukov, Philippe Magaron, and Amy Racine are full time employee at Novartis Pharama AG, Basel, Switzerland; Yuan Xiong was a full time employee at Novartis Pharamceutical Inc., USA.

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Authors' contributions

Andreas Clemens contributed to manuscript writing and concept; Yuan Xiong contributed to the development of the model; Etienne Pigeolet contributed to the model interpretation, manuscript writing and concept; Zufar Mulyukov developed the figures; Philippe Magarone contributed to the manuscript writing and concept; Amy Racine contributed to model interpretation and manuscript writing.

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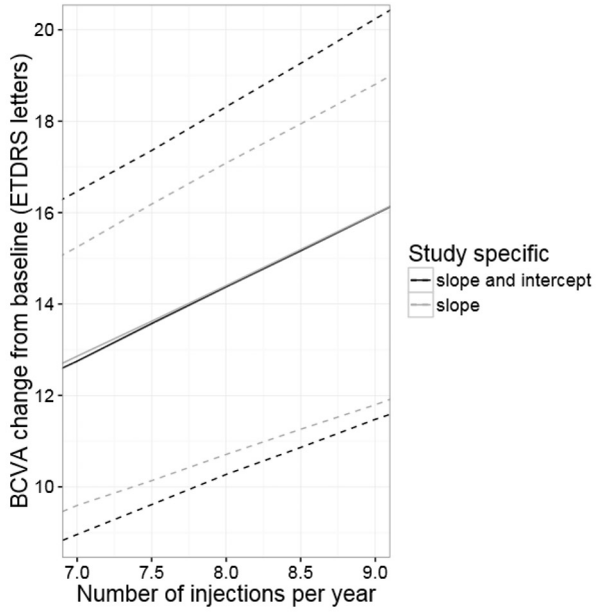

Legend:

BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy score

Predicted VA response
95% prediction interval

Fig. 6. Comparison of efficacy predictions of models with study specific slope (black) and with study specific slope and intercept (grey).

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