The Effects of a Flexible Visual Acuity–Driven Ranibizumab Treatment Regimen in Age-Related Macular Degeneration: Outcomes of a Drug and Disease Model

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PURPOSE. Differences in treatment responses to ranibizumab injections observed within trials involving monthly (MARINA and ANCHOR studies) and quarterly (PIER study) treatment suggest that an individualized treatment regimen may be effective in neovascular age-related macular degeneration. In the present study, a drug and disease model was used to evaluate the impact of an individualized, flexible treatment regimen on disease progression.

METHODS. For visual acuity (VA), a model was developed on the 12-month data from ANCHOR, MARINA, and PIER. Data from untreated patients were used to model patient-specific disease progression in terms of VA loss. Data from treated patients from the period after the three initial injections were used to model the effect of predicted ranibizumab vitreous concentration on VA loss. The model was checked by comparing simulations of VA outcomes after monthly and quarterly injections during this period with trial data. A flexible VA-guided regimen (after the three initial injections) in which treatment is initiated by loss of 5 letters from best previously observed VA scores was simulated.

RESULTS. Simulated monthly and quarterly VA-guided regimens showed good agreement with trial data. Simulation of VA-driven individualized treatment suggests that this regimen, on average, sustains the initial gains in VA seen in clinical trials at month 3. The model predicted that, on average, to maintain initial VA gains, an estimated 5.1 ranibizumab injections are needed during the 9 months after the three initial monthly injections, which amounts to a total of 8.1 injections during the first year.

CONCLUSIONS. A flexible, individualized VA-guided regimen after the three initial injections may sustain vision improvement with ranibizumab and could improve cost-effectiveness and convenience and reduce drug administration–associated risks. (Invest Ophthalmol Vis Sci. 2010;51:405–412) DOI:10.1167/iovs.09-3813

Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland and Genentech, Inc., South San Francisco, CA), an antibody fragment against vascular endothelial growth factor (VEGF), has been shown in clinical trials to stabilize disease progression and to improve vision in patients with neovascular age-related macular degeneration (AMD). In two phase 3 clinical trials, the time course of mean visual acuity (VA) changes seen with monthly ranibizumab injections showed a biphasic pattern. Rapid visual acuity (VA) improvement was seen in most patients during the initial 3 months, followed by a 9-month phase, in which only small further changes in mean VA of approximately 2 letters occurred, compared with the level achieved at the end of the 3-month initiation phase (Fig. 1).1–3

The VA improvements seen during the first three consecutive monthly ranibizumab injections in the MARINA,1 ANCHOR,2 and PIER3 trials—and the differences between monthly and quarterly treatment during the following 9 months of these trials—demonstrate the relevance of the initiation phase, but prompt two key questions for the period after the initiation phase. First, do the available data support the concept of an individualized treatment regimen, based on individual differences in the need for retreatment? Second, if this is the case, can a VA-guided treatment regimen obtain efficacy comparable to that observed with a monthly dose (i.e., on average maintaining the initial VA gain achieved at month 3)?

After the three monthly injections in the initiation phase, the monthly regimen used in MARINA and ANCHOR appeared to be superior to the quarterly regimen used in PIER, in terms of the observed mean VA changes.1–3 However, exploratory analyses of the data from the PIER trial showed that patients could be stratified according to initial gain in VA and maintenance of initial gain (Fig. 2).4 Notably, 40% of patients treated with 0.5 mg ranibizumab maintained their initial gain in VA.

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with the quarterly regimen, providing proof of the principle that initial VA gains can be sustained in some patients with injections given less frequently than monthly.

Variation in individual drug response is a common phenomenon and has been addressed by individualizing treatment or dosage regimens in many diseases such as diabetes and glaucoma.\textsuperscript{5,6} In ranibizumab-treated patients with neovascular AMD, individual drug response is likely to be influenced by many factors that vary within the population. These may include modifying genetic factors,\textsuperscript{7–10} stimuli for VEGF expression, clearance of endogenous VEGF, expression of additional angiogenic and antiangiogenic factors,\textsuperscript{11–14} diet and environmental factors,\textsuperscript{15–25} duration of the disease, and composition of the lesions.\textsuperscript{26,27}

To answer the second question, we considered the following treatment regimen: initial treatment of three consecutive once-monthly 0.5-mg injections, followed by monthly monitoring visits, with further treatment administered if VA decreases by $>5$ letters from the best VA score, with a minimum 1-month interval between treatments. This treatment regimen was targeted to avoid unnecessary injections and potentially improve the treatment benefit/risk ratio (by reducing the attendant risks associated with intravitreal injections) and the convenience and cost-effectiveness of therapy, while ensuring efficacy. To assess the efficacy of this label recommendation in terms of VA outcome, the drug and disease model presented in this article was developed on the basis of the 1-year data from the MARINA, ANCHOR, and PIER trials.
Drug and disease models are valuable tools that complement the evidence obtained from clinical trials by enabling interpolation and/or extrapolation of the available evidence to new concepts. These models are based on the concepts of natural disease progression and the mode of action of the drug. Once developed, the appropriateness of the model is checked by comparing the predicted data from the model with the observed data from clinical trials. Such a modeling and simulation approach has been used to explore treatment effects on cancer progression and on the progression of chronic degenerative disorders such as diabetes, Alzheimer’s disease, and Parkinson’s disease. The approach has also been shown to provide information to help guide the design of additional clinical trials and to supplement information from existing trials.

In this study, we used a drug and disease model of neovascular AMD treated with intravitreal ranibizumab to explore an individualized, flexible regimen after an initiation phase of three once-monthly injections. The results support the concept of the individualization of ranibizumab therapy and serve as a cornerstone for achieving approval of the current European label.

**METHODS**

A drug and disease model for the treatment of neovascular AMD with ranibizumab was developed by using 12-month VA data from three 2-year phase 3 clinical trials (Table 1). All three studies complied with the Declaration of Helsinki. Institutional review board approval of the study protocols was obtained, and the patients provided their informed consent before patient enrollment in each trial.

**Trial Designs and Patient Populations**

Patients treated with ranibizumab received a dose of either 0.3 or 0.5 mg throughout the trials. The MARINA, ANCHOR, and PIER trial designs and patient populations have been reported in detail previously. Briefly, the MARINA and PIER trials compared 0.3 and 0.5 mg ranibizumab against sham injection in the control arm, and the ANCHOR trial compared the same two ranibizumab doses with verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) photodynamic therapy (PDT), which was the previous standard of care treatment for predominantly classic choroidal neovascularization (CNV).

The main inclusion criteria (age ≥50 years, primary or recurrent subfoveal CNV secondary to AMD, and a best-corrected VA of 20/40–20/520) were identical in all three trials. MARINA patients had minimally classic or occult lesions with a maximum lesion size of 12 disc areas; ANCHOR patients had predominantly classic lesions with a maximum lesion size of 5400 μm; and PIER patients had predominantly classic, minimally classic, or occult lesions with a maximum lesion size of 12 disc areas. In ANCHOR, randomized patients had to fulfill the criteria for verteporfin therapy, and thus were expected to require photodynamic therapy in the absence of study drug intervention. Patients with prior verteporfin therapy were excluded. A total of 716 patients were enrolled in MARINA, 423 in ANCHOR, and 184 in PIER. Ranibizumab was administered by monthly intravitreal injections in the ANCHOR and MARINA trials, whereas in the PIER trial, the treatment was administered monthly for three initial consecutive doses followed by a quarterly regimen.

The primary efficacy analyses based on VA were performed at 12 months in all three trials and data from these analyses were used to develop the drug and disease model. For the analyses performed at 24 months in ANCHOR, treatment effect was assessed using a symmetric, two-sided 95% confidence interval (CI) with the assumption that those who were still receiving ranibizumab at 24 months had a VA gain of 12 letters from baseline. The treatment effect was considered significant if the lower bound of the CI was greater than 12 letters.

**Modeling Methods**

The drug and disease model was developed for the period after the initial three once-monthly injections. The analysis of VA in sham-treated patients in MARINA and PIER suggested that it would be appropriate to model the time course of VA without treatment based on the predicted data from the model with the observed data from clinical trials. Such a modeling and simulation approach has been used to explore treatment effects on cancer progression and on the progression of chronic degenerative disorders such as diabetes, Alzheimer’s disease, and Parkinson’s disease. The approach has also been shown to provide information to help guide the design of additional clinical trials and to supplement information from existing trials.

In this study, we used a drug and disease model of neovascular AMD treated with intravitreal ranibizumab to explore an individualized, flexible regimen after an initiation phase of three once-monthly injections. The results support the concept of the individualization of ranibizumab therapy and serve as a cornerstone for achieving approval of the current European label.

**Table 1. Trial Design and Patient Population in Three Phase 3 Randomized Clinical Trials**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ANCHOR</th>
<th>PIER</th>
<th>MARINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>Minimally classic or occult subfoveal lesions</td>
<td>Minimally classic or occult subfoveal lesions</td>
<td>Minimally classic or occult subfoveal lesions</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≥50</td>
<td>≥50</td>
<td>≥50</td>
</tr>
<tr>
<td>Total lesion size</td>
<td>≤12 disc areas</td>
<td>≤12 disc areas</td>
<td>≤12 disc areas</td>
</tr>
<tr>
<td>Baseline mean VA</td>
<td>20/40</td>
<td>20/40</td>
<td>20/40</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>In all studies, concurrent ocular conditions, previous treatment that might compromise assessment</td>
<td>In all studies, concurrent ocular conditions, previous treatment that might compromise assessment</td>
<td>In all studies, concurrent ocular conditions, previous treatment that might compromise assessment</td>
</tr>
<tr>
<td>Schedule</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Treatment</td>
<td>Ranibizumab</td>
<td>Sham injection</td>
<td>Ranibizumab</td>
</tr>
<tr>
<td>Dose</td>
<td>0.3 mg</td>
<td>0.5 mg</td>
<td>0.5 mg</td>
</tr>
</tbody>
</table>
| GLD, greatest linear dimension; SD, standard deviation; VA, visual acuity.
on patient-specific natural progression rates. It was assumed that ranibizumab treatment then altered this natural progression rate in a manner dependent on the vitreous concentration of ranibizumab. Previous pharmacokinetic modeling showed that the concentration of ranibizumab in the vitreous decreases monoeXponentially, with a half-life of 9 days. The effect of vitreous concentration on the change in natural progression rate was described by an $E_{\text{max}}$ model, which is commonly used in pharmacokinetic/pharmacodynamic analyses.21

Quantitative Description of the Drug and Disease Model

The vitreous concentration, $C(t)$, of ranibizumab at time ($t$) after a single injected dose of ranibizumab at time 0 was assumed to be:

$$C(t) = \frac{\text{dose}}{V_{\text{os}}} \times \exp(-k_v \times t)$$

where the vitreous volume was fixed to $V_{\text{os}} = 4 \text{ mL}$, and the rate of systemic absorption was fixed to $k_v = 0.08 \text{ day}^{-1}$, which corresponds to a vitreous elimination half-life of approximately 9 days. The superposition principle was used to characterize vitreous concentration after multiple injections.

The relationship between the disease progression rate and the vitreous concentration of ranibizumab was described by the $E_{\text{max}}$ equation:

$$\text{Progression rate } \left( \frac{\text{dVA}}{\text{dt}} \right) = \frac{\text{max} \times C(t)/(IC_{50} + C(t))}{\text{max}}$$

where $\alpha$ is the patient-specific natural progression rate without treatment, $I_{\text{max}}$ is the maximum possible change in progression rate with ranibizumab treatment, and $IC_{50}$ is the vitreous concentration of ranibizumab where half the maximum possible change in progression rate occurs. As VA is bounded between 0 and approximately 100, the VAs were scaled by a logit transformation before the analyses, to account for floor and ceiling effects (VAs between 20 and 80 are only minimally changed by this transformation).

The model parameters average natural progression rate, $I_{\text{max}}$ and $IC_{50}$, were estimated by using nonlinear least-squares regression based on the time course of the observed average VA results from the ranibizumab-treated patients in ANCHOR, MARINA, and PIER and the sham-treated patients in MARINA and PIER. To estimate the distribution of the natural progression rate of VA in the population of patients with neovascular AMD and to estimate the within-patient variability of VA measurements, we applied a linear mixed-effects model with random intercept and slope to data from the MARINA and PIER sham-treated patients (model fitting by SAS; SAS Institute, Inc., Cary, NC). In accordance with the target of developing a model for the treatment phase after the initial three injections, the treatment-effect parameters $I_{\text{max}}$ and $IC_{50}$ were estimated based only on data during this phase, whereas the estimates of natural disease progression and within-patient variability were based on the complete 1-year data.

Variable-Dosage Scheme Simulation

The drug and disease model was used to simulate a 1-year time-course for the change in VA in 30,000 virtual patients with AMD receiving different types of ranibizumab regimens, while assuming that this treatment followed the standard 3-month initiation phase. The appropriateness of the model was checked by performing simulations in the virtual patients of regimens with monthly injections (as in the MARINA and ANCHOR trials) and quarterly injections (as in the PIER trial), respectively, and comparing the results against the corresponding observed trial data. The distribution of progression rates that were simulated were as observed in sham patients from the MARINA and PIER trials. Subsequently, the model was used to simulate an individualized, flexible VA-guided dosage regimen: after initiation, patients would be monitored with monthly visits, and further treatment would be administered if VA decreases by >5 letters, with a minimum 1-month interval between treatments. Supported by the results of this model, this individualized, flexible VA-guided dose regimen is now recommended within the current European ranibizumab label.37

RESULTS

Mean natural disease progression in VA (model parameter $\alpha$) was estimated as 12.6 letters lost per year (SE $\pm 0.5$). Between-patient variability in natural progression was estimated from the MARINA and PIER sham-treated patients: The between-patients standard deviation of the natural progression was 20 letters per year. The residual within-patient variability was estimated as a standard deviation of 7 letters and was also applied to patients treated with ranibizumab. The model parameter $I_{\text{max}}$, the maximum possible change in progression rate with ranibizumab treatment, was estimated to be 19.3 letters per year (SE 1.4). The vitreous concentration of ranibizumab corresponding to half the maximum effect was estimated as $IC_{50} = 0.0065 \text{ mg/mL}$ (SE 2.7) and was reached approximately 40 days after the last injection.

Observed, quartile data from sham-treated patients in MARINA and PIER were used to define low (5 letters per year), average (12.6 letters per year), and high (19 letters per year) natural disease progression rates. The change in these progression rates (based on the estimated vitreous ranibizumab concentration) was then calculated and is illustrated in Figure 3.

The simulation of monthly and quarterly injections of 0.3 and 0.5 mg ranibizumab and sham injections in 30,000 virtual patients showed a distribution of VA results similar to those observed in the ANCHOR, MARINA, and PIER trials for months 3 to 12 with active treatment and for the entire year with sham injection (Fig. 4). These simulated data, therefore, support this drug and disease model as an accurate description of real-life patient data and as a method for addressing the differences between monthly and quarterly regimens.

After confirmation of its accuracy, the model was used to simulate the alternative dosage strategy of the individualized, flexible, VA-guided treatment regimen. Disease progression and the impact of possible injections were simulated in patients at monthly intervals after the initial three injections. Ranibizumab was administered at a dose of 0.5 mg if a loss of more than 5 letters occurred in comparison with the best-observed VA score for the patient during simulated treatment, including the starting point that reflected initial gain attributable to treatment during the initiation phase. The results indicated that mean VA was stabilized at the approximate level of the initial gain achieved during the first 3 months’ treatment, which is comparable to findings reported with monthly injections in the clinical trials (Fig. 5).

These simulations of the treatment phase after the three initial injections demonstrated that, with this VA-guided approach, on average, VA was stabilized with fewer injections than would occur with a monthly dose. In accordance with observed and corresponding simulated natural disease progression rates, the number of simulated retreatment injections also showed a wide range of values. The simulation predicted that, in this VA-guided treatment regimen, only 7% of the patients with AMD would need 12 injections during the first year; 17% would need 0 to 4 injections; 48% would need 5 to 8 injections; and 35% would need 9 to 12 injections, (Fig. 6). For all subjects together, a mean of 8.1 injections would be needed during the first 12 months of treatment, comprising three initial doses followed by an average of 5.1 doses in months 3 to 11.

DISCUSSION

The concept of an individualized dosage regimen for the treatment of neovascular AMD with ranibizumab was initially
formed based on subgroup analysis of the PIER study results. This analysis demonstrated that some patients can maintain initial improvement in VA with injections given on a quarterly basis (Fig. 2). However, a comparison of data from the ANCHOR, MARINA, and PIER studies shows that, on average, monthly ranibizumab is more efficacious than quarterly treatment. Therefore, the ranibizumab treatment schedule requires optimization to an individualized approach, as the combined results of these three trials suggest that, in some patients, monthly injections would lead to overtreatment and, therefore, unnecessary exposure to treatment risks.

The drug and disease model reported herein for the treatment of neovascular AMD with ranibizumab was designed to evaluate whether an individualized, flexible VA-guided treatment regimen could obtain efficacy comparable to that observed with monthly doses, while at the same time considerably reducing the number of retreatment injections. Together with its corresponding simulations, this approach can be considered as a proof of concept (i.e., a first indication of relevant efficacy) for such an individualized treatment regimen.

Assumptions and Their Possible Impact

Modeling has its limitations and cannot reflect precisely all elements of the disease and the drug effects. In this model, several mostly conservative assumptions were made which could have affected the results of the model, as will now be discussed.
The response to a single injection, in terms of change in the VA natural progression rate, was mainly derived from the month 3 to the month 12 data from the ANCHOR and MARINA studies, and it was assumed that this treatment effect also applies to the VA-guided regimen irrespective of the fact that, in this regimen, a loss of more than 5 letters triggered treatment. After such a vision loss, the response to a single injection might be considerably stronger and possibly closer to effects observed during the initiation phase in the first 3 months of the phase 3 studies; therefore, the approach adopted in this model may be conservative in the sense of overestimating the number of retreatment injections required and underestimating the VA levels reached during the period after the initiation phase. The model also assumed that for patients with a moderate natural disease progression rate, which allows for VA gain, the VA decline that triggers an injection is, in principle, reversible by later treatments. However, this assumption cannot yet be evaluated based on real-life data. For patients with a natural disease progression rate of approximately 20 letters or more, the model suggests that disease progression can only be slowed down and no lost vision can be retrieved. With the VA evaluation-guided treatment regimen, these patients would still be expected to receive their optimal treatment—namely, monthly ranibizumab injections.

The model assumed that the basis for different individual retreatment requirements is the between-subject variability in...
natural disease progression in terms of the number of letters lost in vision per year. The large observed variability in disease progression seen in the control arms of MARINA and PIER suggests that disease progression in AMD is patient-specific. The assumption that the disease progression rate varies only across individuals, but is stable within an individual patient, is also a simplification. For example, the data from the sham-treated groups from MARINA and PIER suggest that there are patients with clinically relevant VA changes occurring only within the space of a few months; but the monthly monitoring visits within the simulated VA-guided regimen ensure that such changes in disease progression can be identified and addressed by early treatment.

The model of a patient-specific natural disease progression rate and its interaction with the concentration of ranibizumab in the vitreous will also have its limitations in patients in whom vision impairment is substantially driven by anatomic changes, such as progressive retinal pigment epithelial dysfunction or atrophy.

Results from pharmacokinetic assessments indicate that differences in the elimination profile of intravitreal ranibizumab between patients are minimal and, therefore, only marginally contribute to the pronounced differences in treatment response. Although identical pharmacokinetics for all patients was assumed, this simplification could also be considered conservative in the sense that the between-subject variability is underestimated and, therefore, the potential benefits of an individualized treatment regimen will also be underestimated. It was further assumed that a patient’s pharmacodynamics mimics his or her pharmacokinetics—namely, that there is no lag time in the return to natural progression after treatment. If such a lag time exists, this could be a source for further between-subject variability.

**Utility of the Ranibizumab Drug and Disease Model**

Despite the assumptions just described, the simulated results from the drug and disease model suggest that it is feasible and effective to individualize ranibizumab treatment based on monthly monitoring of VA. The simulation predicts that during a year of VA-guided therapy, mean VA results over time closely mirror those seen in previous clinical trials with monthly injections, even though the simulation resulted in substantially fewer intravitreal injections. The difference between the monthly regimen and the VA-guided regimen can be estimated to be approximately 3 to 4 letters after 1 year of treatment after the initiation phase. This difference can be mainly explained by the retreatment guidance that requires a patient to experience a loss of at least 5 letters before retreatment.

The individualized, flexible retreatment regimen, based on monthly VA assessment and treatment when the VA declines by more than 5 letters, should provide an approach to further optimize ranibizumab treatment in AMD by specifically addressing over-treatment and its associated risks. A complete comparison of the VA-guided individualized treatment regimen against monthly treatment should take into account all aspects of efficacy, safety, treatment burden, treatment cost, and monitoring expenditures. Such analyses were beyond the scope of this study.

The drug and disease model was developed using simplified assumptions and was fitted to the patients in the MARINA, ANCHOR, and PIER trials, who fulfilled the respective inclusion/exclusion criteria; correspondingly, the conclusions derived from this model are limited to the patient population of these studies. Underlying assumptions, such as an absence of between-patient variability in the intravitreal concentration of ranibizumab in response to a defined dose as well as stable individual natural progression disease rate, mean that the model has a tendency to underestimate variability in the need for retreatment and, therefore, also underestimates the benefit of an individualized flexible treatment regimen. Even with these conservative assumptions regarding between-patient variability, the model predicted considerable variability in the number of injections required during the VA-guided phase, providing strong justification for an individualized treatment regimen with the potential to substantially avoid overtreatment. In addition, it is likely that retreatment after a loss of > 5 letters of VA will show a response similar to that seen during the initial 3 months of treatment, whereas the model only assumed a response as observed during the phase from months 4 to 12 with monthly treatment. With this, the model most probably has a tendency to overestimate the number of treatments required to maintain VA in a clinical setting.

The advantages of flexible dose regimen reported herein is likely to be even greater in clinical practice if the guidance for retreatment could be extended to other disease status assessments, particularly optical coherence tomography (OCT), using both quantitative and qualitative criteria. Detailed results of the SUSTAIN trial (Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration) are eagerly awaited. In SUSTAIN, during the initiation phase, ranibizumab (0.3 mg) was administered monthly for three consecutive months. From month 3 onward, doses were administered if VA decreased by > 5 letters or central retinal thickness was increased by more than 100 μm, with the option to withhold treatment if VA was better than 79 letters or if central retinal thickness was 225 μm or less. OCT may have an important role as a retreatment criterion, as this may be the most sensitive means of detecting VEGF-induced permeability changes. Further drug and disease modeling using VA- and OCT-guided criteria (as for the SUSTAIN trial) may be useful.

**CONCLUSIONS**

In conclusion, VA outcomes data from ranibizumab phase 3 clinical trials, together with the drug and disease modeling results reported herein, support an individualized ranibizumab treatment regimen of three initial once-monthly injections of 0.5 mg ranibizumab followed by monthly monitoring of VA, and retreatment if a VA loss of more than 5 letters occurs, as included on the European label. The simulations predict that using an individualized treatment approach in the clinic would have the potential to reduce overtreatment and its associated risks.

By aggregating knowledge regarding disease progression, pharmacokinetics, and pharmacodynamics, a drug and disease model can be used to assess alternative treatment regimens, providing an essential contribution to drug development. As new information becomes available on both AMD and patients’ responses to treatment, our model can be further refined. Despite all limitations, the model supports the concept that ranibizumab treatment can be further optimized for patients with AMD by individualizing retreatment intervals.

**References**
