Ranibizumab Population Pharmacokinetics and Free VEGF Pharmacodynamics in Preterm Infants With Retinopathy of Prematurity in the RAINBOW Trial

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Received: May 12, 2020
Accepted: June 9, 2020
Published: July 29, 2020

Keywords: ROP; ranibizumab; pharmacokinetics; VEGF

Citation: Fidler M, Fleck BW, Stahl A, Marlow N, Chastain JE, Li J, Lepore D, Reynolds JD, Chiang MF, Fielder AR. Ranibizumab population pharmacokinetics and free VEGF pharmacodynamics in preterm infants with retinopathy of prematurity in the RAINBOW trial. Trans Vis Sci Tech. 2020;9(8):43, https://doi.org/10.1167/tvst.9.8.43

Purpose: To develop a population pharmacokinetic (PK) model for intravitreal ranibizumab in infants with retinopathy of prematurity (ROP) and assess plasma free vascular endothelial growth factor (VEGF) pharmacodynamics (PD).

Methods: The RAnibizumab compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity (RAINBOW) trial enrolled 225 infants to receive a bilateral intravitreal injection of ranibizumab 0.1 mg, ranibizumab 0.2 mg, or laser in a 1:1:1 ratio and included sparse sampling of blood for population PK and PD analysis. An adult PK model using infant body weight as a fixed allometric covariate was re-estimated using the ranibizumab concentrations in the preterm population. Different variability, assumptions, and covariate relationships were explored. Model-based individual predicted concentrations of ranibizumab were plotted against observed free VEGF concentrations.

Results: Elimination of ranibizumab had a median half-life of 5.6 days from the eye and 0.3 days from serum, resulting in an apparent serum half-life of 5.6 days. Time to reach maximum concentration was rapid (median: 1.3 days). Maximum concentration (median 24.3 ng/mL with ranibizumab 0.2 mg) was higher than that reported in adults. No differences in plasma free VEGF concentrations were apparent between the groups or over time. Plotted individual predicted concentrations of ranibizumab against observed free VEGF concentrations showed no relationship.

Conclusions: In preterm infants with ROP, elimination of ranibizumab from the eye was the rate-limiting step and was faster compared with adults. No reduction in plasma free VEGF was observed. The five-year clinical safety follow-up from RAINBOW is ongoing.

Translational Relevance: Our population PK and VEGF PD findings suggest a favorable ocular efficacy: systemic safety profile for ranibizumab in preterm infants.
Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the developing retinal vasculature in preterm infants. The pathophysiology of ROP occurs in two phases: in phase 1, there is a delay in retinal blood vessel development because of the absence of the physiological hypoxic drive that occurs in utero, and in phase 2, the peripheral avascular retina expresses vascular endothelial growth factor (VEGF) into the vitreous. The high levels of VEGF in the vitreous induce pathological angiogenesis; abnormal blood vessels grow into the vitreous, and subsequent glial contraction may cause tractional retinal detachment. Current therapies for ROP are targeted to reduce VEGF levels in the retina and vitreous. While peripheral retinal ablation with a diode laser destroys the VEGF-producing cells, intravitreally injected anti-VEGF antibodies bind to intraocular VEGF.

Ranibizumab is the only approved anti-VEGF agent in this population, based on the randomized, laser-controlled RAnibizumab compared with laser therapy for the treatment of INFants BOrn prematureLy With retinopathy of prematurity (RAINBOW) study. Although several anti-VEGF agents, such as ranibizumab, bevacizumab, and aflibercept (the latter two used off-label) have been used for the treatment of ROP, their pharmacological properties and therefore clinical characteristics differ. In general, systemic exposure to anti-VEGF agents is of concern in preterm infants, as VEGF-dependent developmental processes are underway in many organs. In a population pharmacokinetics (PK) study of intravitreal ranibizumab in adults, vitreous elimination half-life (t1/2) was calculated to be approximately nine days and intrinsic systemic elimination t1/2 was approximately two hours. In contrast, the mean serum t1/2 after intravitreal injection reported in another study in adults was 18.7 days for bevacizumab, 11.4 days for aflibercept, and 5.8 days for ranibizumab. In preterm infants, intravitreal bevacizumab was reported to have a serum t1/2 of 21 days; the serum t1/2 for ranibizumab has not been reported. Only limited information on the VEGF pharmacodynamic (PD) effects of intravitreal anti-VEGF agents in preterm infants is available. There was no systematic effect of ranibizumab on plasma VEGF as observed in the Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity (CARE-ROP) trial and in the RAINBOW study.

Methods

A sparse sampling approach was used for PK and free VEGF PD assessments. PK and free VEGF PD were determined in odd and even numbered ranibizumab-treated patients, respectively, to limit collected blood volume in preterm infants. In addition, free VEGF PD was determined in laser-treated patients. Where possible, the timing of the blood collection coincided with blood collection for other clinical purposes.

PK and PD samplings and analyses in this study were conducted in accordance with the Declaration of Helsinki. Institutional review boards approved the study protocol before the clinical trial was initiated, and parents or guardians of all enrolled subjects provided informed consent.

Determination of Ranibizumab Serum Concentrations

In infants who received initial ranibizumab with an odd subject identification number, blood samples were collected at day 1 (within 24 hours after the first administration), day 15 (days 7–21), and day 29 (days 22–28). The concentration of ranibizumab in the serum was determined using the validated enzyme-linked immunosorbent assay (ELISA) method, in which diluted samples were incubated with a biotin master mix containing biotin-labeled recombinant human VEGF and monoclonal anti-ranibizumab antibodies to form a complex. The sample was then transferred...
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to a streptavidin high-binding ELISA plate, and after washing to remove unbound material, ranibizumab complexes were detected in a colorimetric assay by the addition of horse radish peroxidase (HRP)–conjugated goat anti-mouse immunoglobulin G Fc and tetramethyl benzidine peroxidase substrate. The assay quantification ranged from 0.0150 ng/mL (lower limit of quantitation [LLOQ]) to 0.600 ng/mL in 100% normal human serum.

**Determination of Free VEGF Plasma Concentrations**

In infants who received initial ranibizumab treatment with an even subject identification number plus infants who underwent initial laser therapy, the blood samples were collected at the following time points: day 1 (within 24 hours before the first administration), day 15 (days 7–21), and day 29 (days 22–28).

The concentration of free VEGF (i.e., VEGF that is not bound to ranibizumab) was determined in human K3-ethylenediaminetetraacetic acid (K3-EDTA) plasma samples by an electrochemiluminescence sandwich immunoassay (ECLA) using the V-PLEX Human VEGF Kit (MesoScale Discovery, Rockville, MD, USA). Diluted samples were loaded to wells coated with monoclonal anti-VEGF capture antibodies. Sulfo-tag-labeled anti-human VEGF detection antibodies were added, and the resulting ECLA reaction detected using an MSD reader (MesoScale Discovery). The assay quantification range was from 5.99 pg/mL (lower limit of quantitation, LLOQ) to 253 pg/mL in 100% K3-EDTA plasma.

**Missing Data, Outliers, and Data Exclusions**

Data that were missing and sample concentrations below the LLOQ were treated as missing data. Data from any subject that received an incorrect dose of ranibizumab were excluded. Rescue “switch” to the alternative study treatment was allowed for inadequate treatment response or disease reactivation.9 PK observations from infants who had laser rescue before PK measurement were also excluded for population PK model development. A total of 80, 79, and 174 VEGF concentrations were observed in the ranibizumab 0.1 mg, ranibizumab 0.2 mg, and laser-treated groups, respectively. All free VEGF samples were quantifiable except one sample in the 0.1-mg group on nominal day 15 (actual time nine days). No free VEGF samples were excluded. VEGF observations after ranibizumab-treated infants that were rescued by laser (five samples from four infants; earliest VEGF sample after rescue was 10.6 days after initial treatment) were classified by the laser treatment after the rescue time. VEGF observations after infants were rescued from laser treatment with ranibizumab were also included (10 samples from seven infants; earliest VEGF sample after rescue was 12.2 days after initial treatment) and were classified by the ranibizumab 0.2 mg dose administered at the time of rescue. The patient demographics and clinical samples used for the PK model are summarized in Table 1.

**Base Model without Between-Subject Variability**

The base model was based on the one-compartment model that used the initial estimates from the adult prior model and included the fixed weight-based...
Table 1. Demographics of Infants and Baseline Characteristics (All Patients Receiving Baseline Treatment) Including the Number of Ranibizumab PK and VEGF Observations

|                                | Laser Therapy N = 69 | Ranibizumab 0.1 mg N = 76 | Ranibizumab 0.2 mg N = 73 |
|--------------------------------|----------------------|---------------------------|---------------------------|
| Gestational age at birth, weeks | 26.2 (2.59)          | 26.5 (2.52)               | 25.8 (2.25)               |
| Birth weight, g                | 831 (284)            | 886 (299)                 | 791 (244)                 |
| Postnatal age at baseline, weeks | 10.8 (4.5)          | 11.0 (4.1)                | 11.1 (3.9)                |
| Weight at baseline, median (range), Kg | 1.8 (0.9–4.2)    | 1.8 (0.8–3.8)             | 1.7 (0.8–3.9)             |
| Gender, n (%)                  | Female 35 (50.7)     | 36 (47.4)                 | 33 (45.2)                 |
|                                | Male 34 (49.3)       | 40 (52.6)                 | 40 (54.8)                 |
| Race, n (%)                    | Caucasian 41 (59.4)  | 45 (59.2)                 | 43 (58.9)                 |
|                                | Black 3 (4.3)        | 4 (5.3)                   | 0 (0.0)                   |
|                                | Asian 22 (31.9)      | 21 (27.6)                 | 26 (35.6)                 |
|                                | Other 3 (4.3)        | 6 (7.9)                   | 4 (5.5)                   |
| Number of ranibizumab observations per patient | —                  | 2.7 (0.6)                 | 2.9 (0.6)                 |
|                                | Mean (SD)            | 3.0 (1.0–3.0)             | 3.0 (1.0–5.0)             |
|                                | Median (Range)       | N = 45                    | N = 50                    |
| Number of VEGF observations per patient | 2.8 (0.4)           | 2.9 (0.4)                 | 2.9 (0.8)                 |
|                                | Mean (SD)            | 3.0 (2.0–3.0)             | 3.0 (2.0–3.0)             |
|                                | Median (Range)       | N = 63                    | N = 28                    | N = 27

Data are presented as mean (SD), unless otherwise specified.

*Based on trial full analysis set; N = 74 and 77 for the ranibizumab 0.1 mg and 0.2 mg groups, respectively, and 74 for the laser therapy group.

Because ocular clearance and therefore absorption is the rate-limiting step, as opposed to systemic elimination (also called flip-flop kinetics),22,23 this between-subject assessment of systemic absorption rate (Ka) allows a range of ocular clearances to be inferred from the systemic concentration data.

Addition of Between-Subject Variability

With the base model, between-subject variabilities were added on each estimated population model parameter, as well as possible correlations between these between-subject variabilities as described in Supplementary Table S1. These parameters were added until at least the first-order absorption rate constant (Ka) characterized between-subject variability to more fully characterize the potential individual differences in ocular elimination. Because the model assumes no significant intraocular drug catabolism, and that all ranibizumab eliminated from the vitreous enters the systemic circulation, this systemic absorption parameter Ka equates to the elimination rate constant associated with the ocular clearance of ranibizumab.

Final Model: Description

The final model was defined at the end of the addition of between-subject variabilities. No other covariates were assessed. It was a one-compartment model with first-order absorption rate constant (Ka). Between-subject variability was included on the apparent total body clearance (CL) of bioavailable drug (F; CL/F), apparent volume of distribution (V/F), and Ka terms. The model’s residual variabilities were lognormally distributed.

For clearance from serum (CL) of each infant (CLi), we applied commonly used allometric scaling, prior information about creatinine clearance effect, and infant creatinine clearance (using the modified Schwartz equation; see Supplementary Appendix).
In addition, in this analysis, the apparent volume of distribution in the individual patient was linearly scaled by the infant’s weight. Finally, systemic absorption was related to the ocular concentrations by first-order absorption. Between-subject variability was lognormally distributed on each PK parameter.

Final Model: Parameter Estimates

The model parameters given in Table 2 were derived using allometric scaling from adults to infants. For that reason, the model estimated clearances and volumes for the 70-kg adult values instead of the infant values.

The coefficient of variation is calculated as $100\% \cdot \sqrt{e^{\omega^2} - 1}$, where, because the deviations are lognormally distributed, $\omega$ is the standard deviation of the between-subject variability.

Final Model: Evaluation

To assess goodness-of-fit to observed data of the final model, normalized prediction distribution errors (NPDE) were plotted against expected population predictions (Supplementary Fig. S1) and time (Supplementary Fig. S2). Additionally, individual weighted residuals vs individual predictions (Supplementary Figs. S3 and S5) and time (Supplementary Fig. S4) were plotted. The NPDE versus either the expected population predictions or time after last dose were satisfactory, with no notable trends. A visual predictive check was performed for the 0.1 mg and 0.2 mg ranibizumab doses in the populations for infants, shown in Figure 1. There were no extreme outliers and no trend in either time or concentration that were not adequately captured in the model. The observed data are consistent with the model-based simulations of the data.

The individual post hoc parameters for CL/F and V/F are summarized and presented in Table 3. All the equations for additional PK parameters calculated are presented in the Supplementary Material.

The secondary PK parameters, calculated based on the individual post hoc parameters—maximum concentration ($C_{max}$), time to reach maximum concentration ($t_{max}$), and area under the curve ($AUC$)—were also evaluated for goodness-of-fit.

Figure 1. Final model visual predictive plot of ranibizumab 0.1 mg (a) and 0.2 mg (b).
Table 3. Summary of Post Hoc Predicted and Calculated PK Parameters for Patients Administered Ranibizumab 0.1 Mg and 0.2 Mg Bilaterally

| Parameter                              | Ranibizumab 0.1 mg | Ranibizumab 0.2 mg |
|----------------------------------------|--------------------|--------------------|
| Parameter                              | N = 75             | N = 86*            |
| Apparent V/F, L                        |                    |                    |
| Mean (SD)                              | 1.2 (1.6)          | 1.5 (3.0)          |
| Median (range)                         | 0.8 (0.0–9.5)      | 0.7 (0.0–25.7)     |
| Apparent CL/F, L/day                   |                    |                    |
| Mean (SD)                              | 1.9 (0.7)          | 1.9 (0.8)          |
| Median (range)                         | 1.8 (0.8–5.4)      | 1.7 (0.9–5.6)      |
| Apparent absorption (Ka) t1/2, day     |                    |                    |
| Mean (SD)                              | 5.7 (0.4)          | 5.6 (0.5)          |
| Median (range)                         | 5.6 (4.3–7.0)      | 5.6 (3.7–7.4)      |
| Apparent elimination (K_el) t1/2, day  |                    |                    |
| Mean (SD)                              | 0.4 (0.3)          | 0.4 (0.4)          |
| Median (range)                         | 0.3 (0.0–1.6)      | 0.3 (0.0–3.2)      |
| Tmax, day                              |                    |                    |
| Mean (SD)                              | 1.5 (0.8)          | 1.5 (0.9)          |
| Median (range)                         | 1.3 (0.1–5.8)      | 1.3 (0.1–5.8)      |
| Cmax, ng/mL                            |                    |                    |
| Mean (SD)                              | 12.6 (5.4)         | 26.2 (12.4)        |
| Median (range)                         | 11.5 (3.2–29.0)    | 24.3 (4.3–75.5)    |
| AUCinf, ng/mL*day                      |                    |                    |
| Mean (SD)                              | 119.2 (41.0)       | 240.9 (79.1)       |
| Median (range)                         | 113.6 (37.4–246.7) | 232.0 (70.8–449.1) |

*N includes patients initially treated with and rescued with ranibizumab 0.2 mg. AUCinf = total drug exposure over time; CL/F = clearance of bioavailable drug; Cmax = maximum concentration; t1/2 = half-life; Tmax = time to maximum concentration; V/F = apparent volume of distribution.

concentration (Tmax), and total drug exposure over time (area under the curve, infinity [AUCinf]), are also summarized in Table 3. The PK parameters Cmax and AUCinf were dose proportional.

Effect of Ranibizumab on Plasma Free VEGF Concentrations

The plasma free VEGF concentrations are plotted stratified by actual dose administered (not assigned treatment) and time since first treatment in Figure 2. The median (range) baseline plasma free VEGF level for all samples (n = 104) was 122.5 pg/mL (30.5–959 pg/mL). There were no major differences between the groups and very little trends in time for free VEGF concentrations. This is in line with the summary statistics described in Supplementary Table S2.

To further confirm this finding with the summary statistics, individual predicted concentrations of ranibizumab were calculated and plotted against the observed free VEGF concentrations in the study (Supplementary Fig. S6). No relationship was evident.

Discussion

This is the first PK study of ranibizumab in preterm infants. The final first-order absorption, one-compartment model appropriately captures the systemic PK profile of ranibizumab when injected intravitrealy in preterm infants. The median elimination rate of ranibizumab was 5.6 days (t1/2) from the eye and 0.3 days (t1/2) from serum in these infants. Because vitreous elimination is the rate-limiting step, the apparent t1/2 of ranibizumab in serum after intravitreal administration is equivalent to the vitreous elimination t1/2. The analysis demonstrated no clear relationship between ranibizumab treatment and free VEGF concentrations.

Ranibizumab PK

The PK of ranibizumab has not been described previously in preterm infants. The elimination rate of ranibizumab from the eye was about 50% faster in
Figure 2. Plot of free VEGF concentrations (pg/mL) versus time since first treatment on a semilog scaled stratified by dose. One observation for ranibizumab 0.1 mg after nine days of treatment (nominal day 15) was below the limit of quantitation (<1 pg/mL) and excluded from the plot.

Infants than that reported by Xu et al.\textsuperscript{16} in adults (t\textsubscript{1/2}: 5.6 [infants] vs. 8.6 days [adults]). Furthermore, the elimination rate of ranibizumab from the serum was about three-fold lower than that in adults (t\textsubscript{1/2}: 0.3 vs. 0.09 days).\textsuperscript{16}

Faster elimination from the eye in preterm infants may be due to several factors, including structural differences in tissues, shorter vitreous diffusion pathway within a smaller eye, and reduced blood-retina vessel barrier function in active ROP.\textsuperscript{24} While the methodology used by Xu et al.\textsuperscript{16} was very similar to that used by us, Avery et al.,\textsuperscript{17} using a rather different methodology, reported an adult serum t\textsubscript{1/2} of 5.8 days following intravitreal injection. Xu et al.\textsuperscript{16} studied 674 patients with nAMD whereas Avery et al.\textsuperscript{17} studied 20 nAMD patients within a pool of 43 patients with various pathologies. We believe that the differences in the ranibizumab elimination rate observed between adults and infants in our analysis are not likely due to study variability but a result of the underlying differences between infant and adult morphology and of the pathophysiology of the diseases under study.

As a consequence of an apparent systemic volume distribution, which was about four-fold lower in infants than in adults (as reported by Xu et al.\textsuperscript{16}; median: 0.7–0.8 L vs. typical value: 3.01 L), and an apparent clearance more than 10-fold lower than in adults (median: 1.7–1.8 L/day vs typical population value: 24.1 L/day),\textsuperscript{16} systemic C\textsubscript{max} with a bilateral intravitreal injection of ranibizumab 0.1 or 0.2 mg (per eye) was 7.6- or 16.2-fold higher, respectively, in infants compared to adults receiving ranibizumab 0.5 mg in one eye. In these infants, the median C\textsubscript{max} was about 11.5 and 24.3 ng/mL, in ranibizumab 0.1-mg and 0.2-mg groups, respectively, compared to 1.5 ng/mL in adults.\textsuperscript{16} This was also true for the mean total patient AUC\textsubscript{inf}, which was about five- to 12-fold higher at 119.2 and 240.9 ng \times day/mL compared to 21 ng \times day/mL (Table 3).\textsuperscript{16} These C\textsubscript{max} levels are within the range of IC\textsubscript{50} levels for in vitro endothelial cell proliferation (11–27 ng/mL)\textsuperscript{25,26} and are probably of a relatively brief duration (Fig. 1). Although it is not known whether these C\textsubscript{max} levels have a clinically relevant inhibitory effect on VEGF function outside of the eye, the lack of any demonstrable effect of ranibizumab on plasma free VEGF in our population is reassuring. The short-term rate of systemic adverse events to 24 weeks was not increased in the ranibizumab-treated groups in the RAINBOW trial.\textsuperscript{9} The five-year follow-up extension study is ongoing.

The variability of observed concentrations was higher in infants than in adults, particularly in the estimated volume of distribution. It should be noted that in infants from the RAINBOW study, the range of body weight at treatment varied about fourfold between the lowest and highest weights, which is not the case in an adult population receiving ranibizumab for the treatment of nAMD or other retinal diseases.
The anti-VEGF agents bevacizumab and aflibercept have also been used off-label to treat ROP.27,28 The intraocular PK of bevacizumab and ranibizumab in adults was similar (t1/2 in aqueous: 9.82 and 7.19 days, respectively) after intravitreal injection.23,29 The serum t1/2 after intravitreal injection in adults was 18.7 days for bevacizumab, 11.4 days for aflibercept, and 5.8 days for ranibizumab.17 Ranibizumab is a 48-kDa recombinant monoclonal antibody fragment without Fc domains,30 whereas bevacizumab and aflibercept are larger molecules and contain Fc domains.31 The slower intrinsic systemic clearance of bevacizumab and aflibercept is believed to be due to neonatal Fc receptor (FcRn)–mediated recycling within the endothelial cells, protecting Fc-containing molecules from intracellular degradation.16,17,32 Adequate ocular retention followed by rapid systemic excretion may provide a particularly satisfactory ocular efficacy: systemic safety profile for ranibizumab.

In preterm infants, intravitreal injection of bevacizumab showed dose-related peak serum levels (Tmax) two weeks after injection, a serum t1/2 of 21 days, and persisting detectable levels after 60 days.18 This contrasts with the current study of ranibizumab demonstrating much more rapid systemic ranibizumab elimination, with a Tmax of 1.3 days, a serum t1/2 of 5.6 days, and much reduced serum levels after 28 days.

Our analysis demonstrated no clear relationship between plasma free VEGF and ranibizumab treatment. This finding is consistent with those in the CARE-ROP study, where no systematic effect of ranibizumab on free plasma VEGF was observed.19 Plasma VEGF levels were used to avoid VEGF release from platelets during clotting to better reflect true free VEGF;33 VEGF levels measured in serum tend to be higher than those in plasma, and studies in which serum VEGF was measured should be interpreted with caution.34 Serum VEGF was unchanged in four preterm infants after ranibizumab treatment but was reduced after bevacizumab treatment.18,35 Other studies demonstrated sustained reduction of serum VEGF in preterm infants after intravitreal injection of bevacizumab; serum VEGF levels remained low for at least 12 weeks and a negative correlation between serum VEGF and serum bevacizumab has been demonstrated.35,36 Similarly, in adults following intravitreal injection of aflibercept34,37 or bevacizumab,17 plasma free VEGF fell rapidly and remained low for at least 30 days, with aflibercept causing the greatest depression. In contrast, there were no significant changes after ranibizumab treatment.17,34,37

We observed higher baseline levels of plasma free VEGF in preterm infants with ROP than those previously reported in adults with nAMD or retinal vascular disease. Combining our baseline plasma free VEGF levels in the three treatment groups (n = 104), the median (range) was 122.5 pg/mL (30.5–959 pg/mL). This compares with a mean value of 17.0 pg/mL in adults with nAMD.17 The difference may be due to the presence of ROP and physiological angiogenesis processes taking place in infants.3 However, there were minor analytical differences between these studies, and direct comparison should be treated with caution.

The RAINBOW trial was performed in 26 countries and was the largest trial to date of an anti-VEGF agent for ROP.9 Serum ranibizumab and plasma free VEGF sampling was an integral part of the trial. The study was much larger than the previous studies of anti-VEGF PK in preterm infants and of ranibizumab-related plasma VEGF PD. Sparse sampling, necessary to limit blood loss and stress in fragile preterm infants, inevitably limited the number of samples available. It is possible that our limited data did not show a relationship between ranibizumab exposure and plasma free VEGF that was in fact present. The lack of paired samples, high intersubject variability, a spread of sampling times, and a limited number of samples mean that we cannot rule out such a relationship.

In conclusion, ranibizumab PK was different in preterm infants than in adults. This difference was not accounted for by allometric scaling alone but required estimation of different PK parameters using the PK data from the RAINBOW study. Elimination of the drug from the eye was the rate-limiting step and was about 50% faster in preterm infants compared to adults. After bilateral intravitreal administration, the estimated t1/2 in the eye was about 5.6 days, and the estimated t1/2 of ranibizumab in systemic circulation was 0.3 days. Overall circulating ranibizumab concentrations in the studied population were higher than those in adults, related to the different proportion of ocular volume: body weight in infants. No clear systematic reduction in plasma free VEGF levels was observed. We demonstrated no relationship between predicted systemic ranibizumab concentrations and observed systemic plasma free VEGF concentrations. Our population PK and VEGF PD findings suggest a favorable ocular efficacy: systemic safety profile for ranibizumab in preterm infants. Clinical evidence of the long-term systemic safety of intravitreal ranibizumab must await the five-year patient data, but the short serum t1/2 of ranibizumab coupled with the absence of an effect on plasma free VEGF is reassuring.
Acknowledgments

The authors thank Daniel Stiehl, MD, (Novartis Pharma AG, Basel, Switzerland) for his expert input on patient safety aspects of the study and for critical review of the manuscript. The authors also acknowledge the editorial support (including compilation and addressal of comments from authors) provided by Lakshmi Deepa Gurajala, PhD, of Novartis Healthcare Pvt. Ltd., Hyderabad, India, which was funded by Novartis Pharma AG, Basel, Switzerland. The RAINBOW study investigators (Supplementary Appendix Table S3) lead activity in the study centers and contributed data.

Supported by Novartis Pharma AG.

Disclosure: M. Fidler, Novartis (E); B.W. Fleck, Novartis (C); A. Stahl, Novartis (R), Allergan (C), Bayer (C), Novartis (C); N. Marlow, Novartis (C); J.E. Chastain, Novartis (E); J. Li, Novartis (E); D. Lepore, Novartis (C); J.D. Reynolds, Novartis (C); M.F. Chiang, Novartis (C), IntiTeleretina, LLC (I), Research to Prevent Blindness (R), NIH grant P30EY10572 (R); A.R. Fielder, Bayer (C), Novartis (C)

† List of RAINBOW study investigators can be found in the supplementary appendix.
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