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ARTICLE

Pharmacokinetic-pharmacodynamic modelling of the anti-FcRn monoclonal antibody rozanolixizumab: Translation from preclinical stages to the clinic

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Abstract

Rozanolixizumab is a fully humanized high-affinity anti-human neonatal Fc receptor (FcRn) monoclonal antibody (mAb) that accelerates the removal of circulating immunoglobulin G (IgG), including pathogenic IgG autoantibodies, via the natural lysosomal degradation pathway. The aim of this study was to develop a pharmacokinetic/pharmacodynamic (PK/PD) model characterizing the effect of rozanolixizumab on IgG levels in cynomolgus monkeys, translate it into humans to support the first-in-human (FIH) rozanolixizumab clinical trial study design, and, ultimately, develop a PK/PD model in humans. Simulations from the preclinical model were performed to predict IgG responses in humans and select clinically relevant doses in the FIH study. Good alignment was observed between predicted and observed reductions in IgG, which increased with increasing dose in the FIH study. The model successfully described the PK of the 4 and 7 mg/kg intravenous (i.v.) dose groups, although the PKs were underpredicted for the 1 mg/kg i.v. dose group. Updating the model with subsequent human data identified parameters that deviated from preclinical assumptions. The updated PK/PD model was able to effectively characterize the PK FcRn-IgG nonlinear system in response to rozanolixizumab in the FIH data.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

To date, there have been no established semimechanistic models that could be used to translate pharmacokinetic/pharmacodynamic (PK/PD) responses to an anti-human neonatal Fc receptor monoclonal antibody-based therapeutic from preclinical data to humans.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can we create a useful PK/PD model to predict responses to single i.v. doses of rozanolixizumab in humans, based on in vitro data, in vivo data, and knowledge from literature?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This PK/PD model accurately predicted responses to rozanolixizumab in humans, especially at 4 and 7 mg/kg doses from preclinical species. Adjusting model

parameters to include rozanolixizumab first-in-human data refined the model further and showed good predictive performance.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The prediction of rozanolixizumab responses in humans using this PK/PD model has informed future clinical trial design; the model is being further updated as more clinical data is available and will be used to examine hypotheses related to other aspects of disease management and treatment.

INTRODUCTION

Pharmacokinetic (PK) and pharmacodynamic (PD) modeling is an important tool to support the translation of novel therapeutics from preclinical to clinical research.[1–4] PK/PD models are efficient summaries of drug-related information that support drug development decision making and reduce the risk of development failures.[5,6] They reflect the biological distribution of the compounds and targets under investigation as closely as possible.[2] Initial preclinical models often involve allometric scaling based on assumed physiological similarities between animal species.[7] Once a first-in-human (FIH) study has been initiated, early PK/PD data can be incorporated into such models in an integrative process that can improve dose escalation and subsequent study design processes.[1,6]

The long half-life of immunoglobulin G (IgG) is due to the action of the neonatal Fc receptor (FcRn), which efficiently binds IgG at the acidic pH of the endosome and recycles it back to the cell surface to be released into the circulation, rather than being catabolized in the natural lysosomal degradation pathway.[8] Rozanolixizumab is a fully humanized, high-affinity anti-human FcRn monoclonal antibody (mAb).[9] It is designed to specifically target the IgG-binding region of FcRn, binding with high affinity and acting as an inhibitor of IgG recycling, leading to accelerated catabolism to reduce concentrations of circulating IgG.[9] Rozanolixizumab therefore has potential as a treatment for patients with autoimmune diseases driven by circulating pathogenic IgG autoantibodies, such as immune thrombocytopenia (ITP) and myasthenia gravis (MG).[8,10] In vivo characterization of rozanolixizumab in both a human FcRn transgenic mouse model and in cynomolgus monkeys demonstrated dose-dependent reductions in plasma IgG concentration, and rapid clearance of the drug with nonlinear PKs indicative of target-mediated drug disposition (TMDD).[9]

The present study aimed to develop a translational PK/PD model of the IgG response to rozanolixizumab treatment in humans, based on preclinical responses[9] and assumptions from other in vitro investigations and literature reports. A population nonlinear mixed effects (NLME) PK/PD modeling approach was used to determine the relationship between IgG response and rozanolixizumab concentration, and to quantify IgG response over time. The PK/PD model was used in the rozanolixizumab drug development program to optimize the design of a FIH study,[11] and the FIH data were used to further refine the model.

METHODS

Application of PK/PD data obtained in cynomolgus monkeys for development of a semimechanistic PK/PD model

Plasma levels of total IgG, rozanolixizumab, and anti-drug antibodies (ADAs) directed against rozanolixizumab were previously determined in vivo, following single- or multiple-dose intravenous (i.v.) rozanolixizumab infusions (5, 10, or 30 mg/kg) in cynomolgus monkeys.[9] The ADAs were detectable in the majority of animals during the dosing period; however, no impact on PK or PD was observed.[9] Only single-dose i.v. data were used for modeling; multiple-dose data before ADA detection were used for external validation.

A two-compartment model with TMDD[1,12] was used to describe rozanolixizumab PKs, and an indirect-effect model to describe IgG concentration changes. This simplification of the complex FcRn-IgG-rozanolixizumab relationship required structural assumptions. First, the original TMDD model was designed for drugs that bind to a target on the surface of cells that are freely circulating.[12] For the current model, FcRn was assumed to be proximate to the blood compartment due to its high expression on the surface of vascular endothelial cells.[10] The endosomal compartment was hence combined with the central compartment, assuming endothelial cells were kinetically indistinguishable from plasma space where rapid binding and equilibrium was assumed to occur, similar to the assumptions made by Kim et al. 2007.[13] Second, FcRn has a high observed affinity for the Fab portion of rozanolixizumab,[9] whereas binding of the rozanolixizumab Fc domain is weak at neutral pH[9] in line with weaker binding

of the Fc region of cynomolgus monkey IgG to FcRn.[14] Therefore, the model assumed that it is the Fab portion of rozanolixizumab which binds FcRn, and hence blocks its own recycling process of the free format back into the plasma compartment. The differential equation for the two-compartment target binding model, with respect to the total drug antibody (TA) in the central and peripheral (APERI) compartments, is detailed in Supplementary Text S1. Central volume (V), peripheral volume (V2), intercompartmental flow of free drug between V and V2 (Q), clearance of free drug (CLA), clearance of drug:target complex (CLB), target production rate (RB) and equilibrium binding constant (KD) were estimated in the model, and interindividual variability (IIV) terms were assessed if possible.

An indirect-effect model[15] was used to describe the effects of rozanolixizumab on elimination of total IgG over time. The concentration of free rozanolixizumab was assumed to drive this effect, in line with the mechanism of action. The differential equation describing this process is shown in Supplementary Text S2.

A population NLME modeling approach was utilized in this study, and the population model structure, including IIV or residual variability, is further detailed in Supplementary Text S3.

Development of a cynomolgus monkey-to-human-translated PK/PD model

Translation from cynomolgus monkey to humans used a combination of allometric scaling techniques, in vitro, and literature data. Assumptions used to inform simulations in the PK/PD model parameter translation from cynomolgous monkeys to humans are summarized in Table 1. In vitro affinity (KD) data using purified proteins were generated during functional characterization of rozanolixizumab using surface plasmon resonance (SPR) in human and cynomolgus monkeys.[9] Additionally, Madin-Darby canine kidney (MDCK) cells transfected with either human or cynomolgus monkey FcRn were used to assess rozanolixizumab binding to FcRn at the cell membrane level.[9] These in vitro data were then used to translate the in vivo KD estimated from the cynomolgus monkey study into humans, as described in Table 1.

Application of cynomolgus monkey-to-human-translated PK/PD model to optimize FIH design and guide dose escalation

Simulations were performed of possible scenarios for a subsequent FIH study.[11] The percentage change from baseline IgG was simulated from the translated monkey-to-human PK/PD model following a range of single i.v. doses of rozanolixizumab. Initially five i.v. doses were selected to achieve a dose response of 50–60% decrease in IgG, similar to that observed following plasma exchange treatment.[16–18] However, rozanolixizumab was halted at 7 mg/kg because the adverse event profile did not support further i.v. escalations in healthy subjects,[11] and s.c. dosing was then explored. Therefore, data are shown for the first three planned i.v. doses only (1, 4, and 7 mg/kg).[11]

Simulations accounted for IIV and uncertainty in the translated PK/PD parameters, as specified in Table 1, in order to optimize the FIH study design. Briefly, 800 PK/PD vector parameters were simulated in R (version 3.0.1) using the Metrum software package version 5.05 (Metrum RG, Metrum Research Group). This generated 800 NONMEM control streams using the translated PK/PD typical parameter values, and simulations included the uncertainty on fixed effects and IIV. Stochastic Monte Carlo simulations were performed for each parameter vector in NONMEM 7.3 (ICON Development Solutions) for each dose cohort following single i.v. infusions at different doses.

Update of the monkey-to-human translated PK/PD model with FIH data

The monkey-to-human-translated PK/PD model was updated with final FIH study data[12] to enable optimization of future proof-of-concept (POC) studies. Prior functionality (NWPRIOR in NONMEM) was used to inform the estimation process during dose escalation as new data were included to inform the model.[19] As data were generated, the number of priors required to support the estimation process of parameters was reduced.

In the final human PK/PD model, priors in FcRn, V2, Q, and KD were retained (Table 2) in NONMEM, and the first-order conditional estimation (FOCE) algorithm was used. The halting of dose escalation at the 7 mg/kg dose in the FIH study[11] led to a lower range of dose coverage to inform the PK/PD model than originally anticipated. Data were obtained from both i.v. and s.c. doses in the FIH study,[11] although for modeling purposes and comparison to the monkey-to-human translated PK/PD model (based on i.v. data), only the analysis of i.v. cohorts from the FIH study are presented.

Model evaluation

Standard diagnostic methods were used to assess model performance, including improvement in objective function value (OFV), goodness of fit plots, and visual

TABLE 1 Assumptions used in the PK/PD model parameters translation from cynomolgus monkeys to human to inform simulations

Parameter		Cynomolgus monkey estimated typical mean value	Human translated mean value	IIV human (CV %)	Uncertainty (RSE %)	Translation reference and assumptions
PK (TMDD)	V (L)	0.108	2.55	16.35	–	• TV allometrically scaled • Cynomolgus monkey PK parameters were translated into humans using allometry for a 75 kg subject (V, Q, V2, and CLA), and the formula used is detailed in Supplementary Text S4 • IIV from in-house mAb
	Q (L/day)	0.0221	0.237	–	–	
	V2 (L)	0.0162	0.383	28.75	–	
	CLA (L/day)	0.0709	0.7605	35.15	–	
	KD (nM)	0.827 (cells exp. in vitro ~ 1 nM)	0.359	–	58.0	• TV translation to human based on in vitro (MDCK cell) differences in binding affinity (KD) using purified proteins, where there was a slightly higher affinity for human-expressed FcRn compared with cynomolgus monkey FcRn[9] • SPR data demonstrated a similar affinity for FcRn receptors in cynomolgus monkeys and humans,[9] therefore uncertainty in KD translation was based on the difference of KD_{human}/KD_{cyno} ratios at different pHs, between SPR and MDCK cell experiments (RSE of 58% assumed)[9]
	RB (nmol/day) In model for simulation: $RB = [FcRn]^{*}K_{deg}{}^{*}V$	21.7 $[FcRn]^{a}$ = 592.89 nmol/L	419.748 $[FcRn]^{a}$ = 592.89 nmol/L	–	–	• In the cynomolgus monkey PK model, RB of FcRn was estimated at 592.89 nM • Same FcRn concentration assumed for monkey and human (0.6 μM): based on comparisons of data from in vitro expression experiments in PBMCs from cynomolgus monkeys and humans (UCB, data unpublished) and current literature on PBPK models[27,33,38,39]
	CLB (L/day) In model for simulation: $CLB = K_{deg}{}^{*}V$	CLB = 0.0366 $K_{deg}{}^{a}$ = 0.3389 (day^{-1})	CLB = 0.7079 $K_{deg}{}^{a}$ = 0.277 (day^{-1})	18 (in K_{deg})	47.28 (in K_{deg})	• K_{deg} translated as a weighted mean, assuming it was similar to the cynomolgus monkey estimate of 0.3389 day^{-1} or was allometrically scaled to 0.1536 day^{-1} • This former assumption was given an 85% weight, as it has been commonly used in PBPK modeling when incorporating the FcRn system.[30] • Uncertainty was based on the difference between these two hypothetical values • IIV from literature for other receptors[7,46]

TABLE 1 (Continued)

Parameter		Cynomolgus monkey estimated typical mean value	Human translated mean value	IIV human (CV %)	Uncertainty (RSE %)	Translation reference and assumptions
PD	IgG base (mg/ml)	10.5	11.65	21	–	• Literature[47,48]
	K_{out} (day^{-1})	0.0431	0.031	22	21.48	• TV translated into human by averaging between the allometrically scaled value from the estimated cynomolgus monkey K_{out} 0.02 day^{-1} as described in Kagan et al. 2010[46] for a different system, and the reported value from literature for endogenous IgG based on typical estimated half-lives that range between 18–23 days[47,49] • Uncertainty from the difference between literature and allometrically scaled parameter • IIV from literature[47]
	E_{max}	7.58	7.58	25	43	• E_{max}, and therefore the maximum capacity of rozanolixizumab to accelerate IgG elimination, was assumed to be the same in cynomolgus monkeys and humans[47] • Uncertainty from differences between expected maximum effect based on humans lacking FcRn[41] and considering the same value estimated in monkeys • IIV based on literature[46]
	EC_{50} (mg/L)	1.14	0.4959	58	66	• EC_{50} (concentration of rozanolixizumab that corresponds to 50% maximal IgG catabolism) estimated from cynomolgus monkeys was corrected in a similar manner to KD across cynomolgus monkeys and humans, based on KD in vitro differences (MDCK cells) • Uncertainty from difference between this value and considering the same EC_{50} as in cynomolgus monkeys • IIV from in-house trial for a different system and literature for another biomarker

Abbreviations: CLA, clearance of free drug; CLB, clearance of drug:target complex assumed to be the same as for target; CV, coefficient of variation; EC_{50}, concentration of rozanolixizumab that corresponds to 50% maximal IgG catabolism; E_{max}, maximum effect; FcRn, neonatal Fc receptor; IgG, immunoglobulin G; IIV, interindividual variability; KD, equilibrium binding constant; K_{deg}, degradation rate constant; K_{in}, IgG production rate constant; K_{out}, IgG elimination rate constant; PD, pharmacodynamic; PK, pharmacokinetic; Q, intercompartmental flow of free drug between central and peripheral compartments; RB, target production rate; RSE, relative standard error; SPR, surface plasmon resonance; TMDD, target mediated drug disposition; TV, typical value; V, central volumes; V2, peripheral volumes.

[a]Parameter estimated in cynomolgus monkeys was transformed into this form for translation and simulation purposes.

TABLE 2 Final PK/PD parameters, based on the FIH data[11]

Parameter		Human translated parameters	FIH estimated parameters (RSE %)
PK (TMDD)	V (L)	2.55	2.7 (6.3)
	Q (L/day)	0.27	0.271[a] (16.6)
	V2 (L)	0.383	0.36[a] (20.8)
	CLA (L/day)	0.7605	0.968 (6.8)
	KD (nM)	0.359	1[a] (14.6)
	[FcRn] (nM)	592.8	147[a] (14.4)
	RB nmol/day RB = [FcRn]*Kdeg*V	419.748[b]	349.3[b]
	K_{deg} (day^{-1})	0.227	0.88 (15.5)
	Prop RE (CV %)	–	9.3 (7.4)
	IIV V (CV %)	16.35	15.8 (21.2)
	IIV K_{deg} (CV %)	18	30.3 (18.1)
PD	IgG base (mg/ml)	11.65	9.88 (1.8)
	K_{out} (day^{-1})	0.031	0.0364 (4.4)
	E_{max}	7.58	4.24 (5.5)
	EC_{50} (mg/L)	0.4959	0.154 (15.3)
	IIV IgG base (CV %)	21	18.4 (18.7)
	Prop RE (CV %)	–	5.8 (2.6)

Abbreviations: CLA, clearance of free drug; CLB, clearance of drug:target complex assumed to be the same as for target; CV, coefficient of variation; EC_{50}, concentration of drug producing 50% of stimulation of IgG catabolism; E_{max}, maximum effect; FcRn, neonatal Fc receptor; IgG, immunoglobulin G; IIV, interindividual variability; KD, equilibrium binding constant; K_{deg}, degradation rate constant; K_{out}, IgG elimination rate constant; PD, pharmacodynamic; PK, pharmacokinetic; Prop RE, proportional residual error; Q, intercompartmental flow of free drug between central and peripheral compartments; RB, target production rate; RSE, relative standard error; TMDD, target mediated drug disposition; V, central volumes; V2, peripheral volumes.

[a]Parameter estimated with prior information in the final model.

[b]Derived value (not estimated).

predictive checks (VPCs). Prediction-corrected VPCs were used to verify that the model predicted both the central tendency and variability in the observed data. The final model parameter estimates (theta [θ], eta [η], and epsilon [ε]) were used to simulate replications of the original dataset. The model's predictive performance was evaluated based upon the following criteria. Approximately 90% of the observed concentrations' values fall within the 5th and 95th percentiles of the simulated concentrations, and observed values do not exhibit any systematic and substantial bias with respect to the median of the simulated values.[20] Additionally, in the initial cynomolgus monkey model, the multiple dose data before ADA detection were used for external validation of the model through simulations.

Software and statistical analysis

Simulations of the FIH design were undertaken using NONMEM version 7.1.2 (ICON Development Solutions), and the Metrum software package version 5.05 within R (MetrumRG, Metrum Research Group).

Cynomolgus monkey data were analyzed using NONMEM version 7.1.2 (ICON Development Solutions). FIH data were analyzed by nonlinear mixed-effects modeling, with the FOCE method, using NONMEM version 7.3 (ICON Development Solutions).

Graphs of the simulations from monkey-to-human, and the overlay of human data, were undertaken using R. VPCs were run using Perl-speaks NONMEM (PsN) for monkey VPCs (version 3.2.12) and FIH VPCs (version 4.2.0).[21,22] VPC graphs were generated using the xpose 4[23] package in R.

RESULTS

Development of a preclinical PK/PD model and human translation

The PK/PD relationship in cynomolgus monkeys was characterized as a two-compartment model with TMDD in the central compartment and an indirect-effect model, where the free drug stimulates IgG catabolism. Figure 1 shows a schematic representation of the structural PK/PD model. Table 1 details assumptions, parameter estimates, and uncertainties in the translation from cynomolgus monkeys to humans. Observed PK and percentage changes from baseline IgG following single i.v. doses of 5, 10, and 30 mg/kg are shown in Figure S1. The VPCs for the single i.v. doses of 5, 10, and 30 mg/kg, and simulation of the loading i.v. dose of 30 mg/kg followed by 42 daily i.v. doses of 5 mg/kg (Figure S2) served as external validation of the derived PK/PD cynomolgus model; for the latter, the VPCs were truncated up to the point where ADAs were detected. The preclinical PK/PD model derived from single-dose administration of rozanolixizumab in cynomolgus monkeys successfully described multiple administrations in cynomolgus monkeys. However, at approximately day 12, the PKs were overpredicted by the model, which translated in the IgG effect.

Application of the translated model for optimization of FIH study design and dose escalation

Stochastic Monte Carlo simulations were performed for different rozanolixizumab doses, accounting for

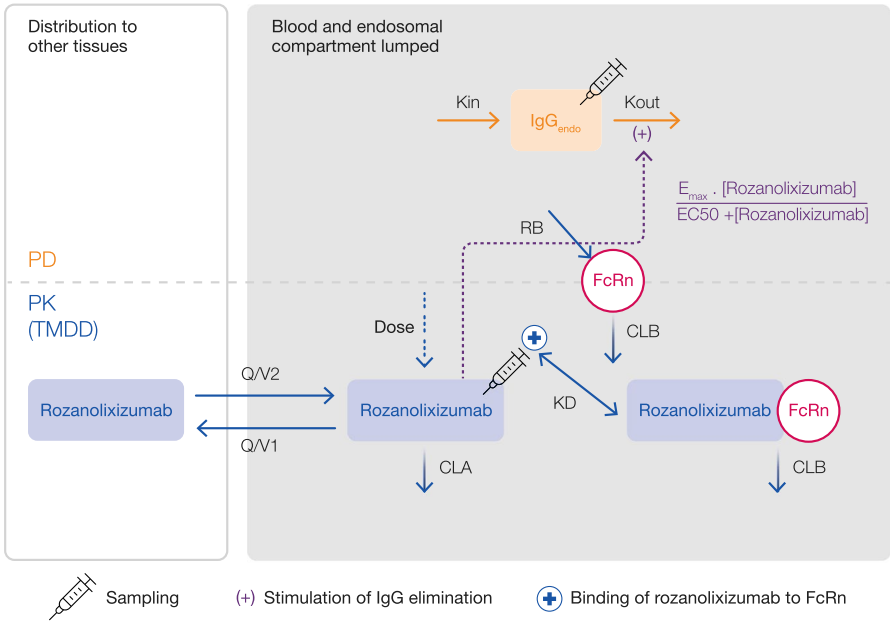

FIGURE 1 Schematic representation of the structural PK/PD model. Rozanolixizumab pharmacokinetics are described by a two-compartment model with TMDD using the quasi-equilibrium approximation in the central compartment. The effects of rozanolixizumab on IgG are described by an indirect-effect model, where the free drug stimulates IgG catabolism through an E_{max} model. CLA, clearance of free rozanolixizumab; CLB, clearance of rozanolixizumab:target complex assumed to be the same as for target; EC_{50}, concentration of rozanolixizumab that corresponds to 50% maximal IgG catabolism; E_{max}, maximum effect; IgG, immunoglobulin G; KD, equilibrium binding constant; K_{in}, IgG production rate constant; K_{out}, IgG catabolic rate constant; PD, pharmacodynamic; PK, pharmacokinetic; Q, intercompartmental flow of free rozanolixizumab between central and peripheral compartments; RB, target production rate; TMDD, target mediated disposition; V, central volumes; V2, peripheral volumes

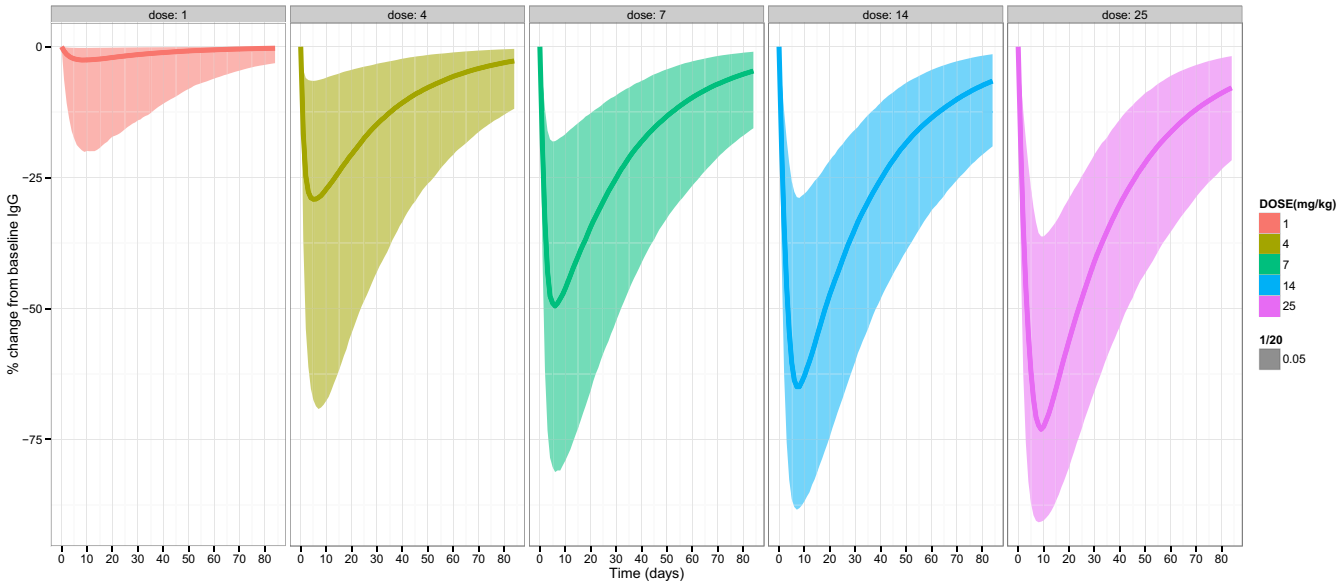

FIGURE 2 Predicted median (solid line) with ±90% prediction interval percentage change from baseline in IgG following a single i.v. dose of rozanolixizumab in humans

uncertainty in the translation and providing a range of IgG reductions to assess the dose-response relationship with IgG decrease. Simulations aimed to achieve 50–60% baseline IgG reductions. The median and 90% prediction interval were calculated and represented from these simulations for the different doses (Figure 2). At the lowest concentration tested (1 mg/kg), a less than 10% reduction from baseline in median IgG was predicted, corresponding to the minimum anticipated biological effect level following rozanolixizumab administration. The

doses for assessment in the FIH study[11] were selected and guided by these simulations.

Update of cynomolgus monkey-to-human-translated PK/PD model with clinical data

In the FIH study, mean reductions in IgG of 14.5, 33.4, and 47.6% (10 days postdose) were observed for the 1, 4, and 7 mg/kg rozanolixizumab doses, respectively.[11] Figure 3 shows the rozanolixizumab FIH individual observations versus the initial predictions from the translated PK/PD model for (A) percentage change from baseline in IgG versus time, and (B) rozanolixizumab concentration versus time. Prediction/observation alignment increased at higher doses, as the system moved towards linearity for both PK and IgG.

A comparison between the human translated and the final estimated parameters based on the FIH study i.v. data[11] is shown in Table 2. The PK linearly related parameters were well-translated by allometry, whereas some differences were observed between cynomolgus monkeys and humans in the parameters driving the TMDD process. Updating the final human PK/PD model with human data identified five parameters that deviated from preclinical assumptions: FcRn concentration, KD, first order degradation (K_{deg}), maximum effect (E_{max}), and half-maximal effective concentration (EC_{50}). In addition, some

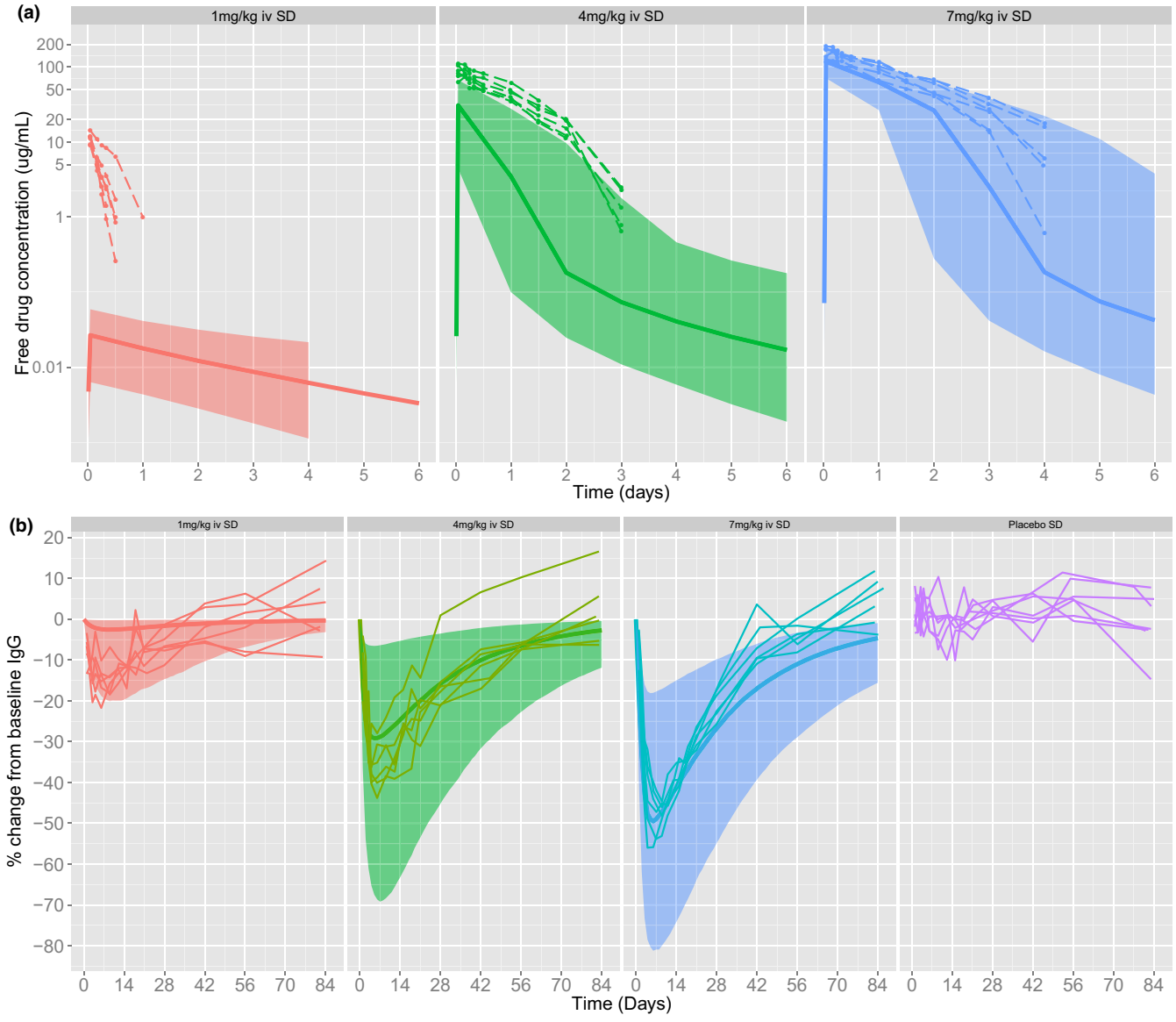

FIGURE 3 Rozanolixizumab FIH observations (thin lines, a; dotted lines, b) and median (solid line) with ±90% prediction intervals translated PK/PD model simulations for (a) percentage change from baseline in IgG versus time, and (b) rozanolixizumab concentration versus time. The observed concentration in terms of PK and PD data were superimposed graphically with the 5th percentile, median, and 95th percentile of the simulated PK and IgG concentrations. FIH, first-in-human; PK/PD, pharmacokinetic/pharmacodynamic

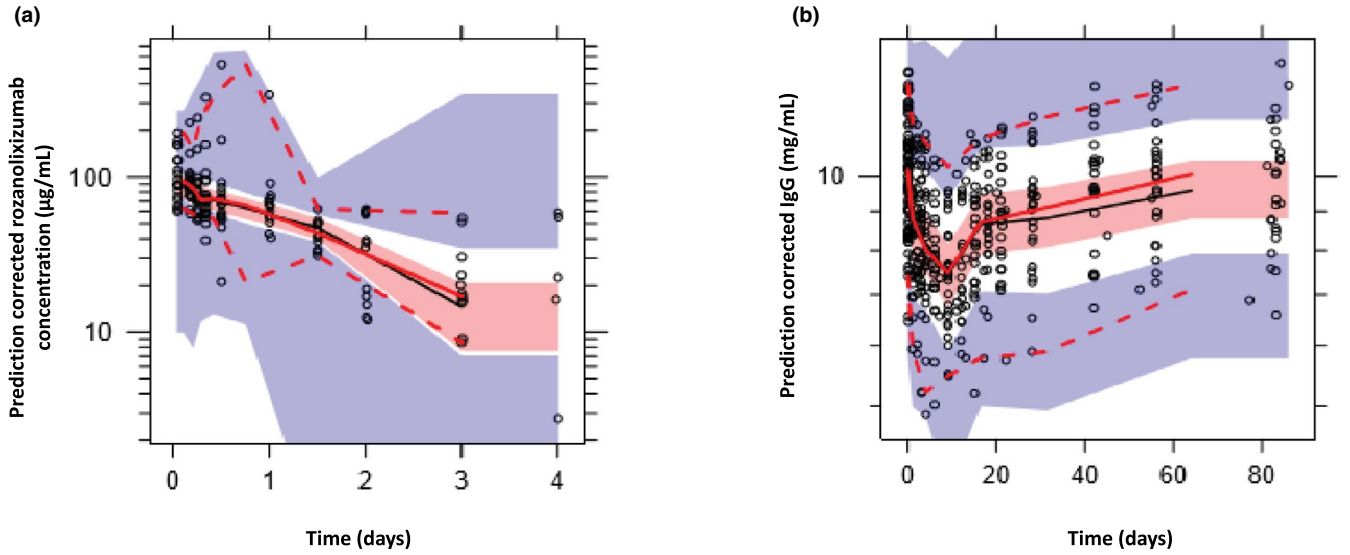

FIGURE 4 Prediction-corrected VPC (a) rozanolixizumab concentration versus time (µg/ml), and (b) IgG concentration versus time (mg/ml), following single i.v. administration of rozanolixizumab in the FIH study.[11] The 50th percentile of the simulation (1000 simulations) is denoted by a solid black line; 50th percentile of the observed data is denoted by a solid red line; the 2.5th and 97.5th percentiles of the observations are denoted by dashed red lines. The red shaded area corresponds to the 95% CI around the 50th prediction interval, the blue shaded area corresponds to the 95% CI around the 2.5th and 97.5th percentiles of the simulations. CI, confidence interval; FIH, first-in-human; VPC, visual predictive check

parameters (FcRn concentration, KD, V2, and Q) required support from the preclinical translated model in order to stabilize the model (Tables 1 and 2).

Prediction-corrected VPCs (Figure 4) confirmed that the final model adequately described PK/PD data in humans following i.v. rozanolixizumab. However, whereas the model successfully described the 4 and 7 mg/kg dose groups, VPCs suggest the PKs were underpredicted for the 1 mg/kg group. The description of the 1 mg/kg dose in humans with the final human PK/PD parameters was improved, although still underpredicted by the final model (data not shown).

DISCUSSION

We have developed a semimechanistic translational PK/PD model of the IgG response to the anti-FcRn mAb rozanolixizumab in humans based on preclinical in vivo data in cynomolgus monkeys,[9] and utilized it to successfully predict PK and IgG effects in humans. Dose-dependent concordance was seen between model predictions and observations,[11] and the model correctly characterized a nonlinear and complex system in a simplified mathematical description. This model is able to reflect the underlying mechanism of action of rozanolixizumab through inhibition of IgG recycling from endosome to plasma (driven by free concentration of rozanolixizumab), and where rozanolixizumab binds FcRn for several recycling cycles until it is eliminated.[9] The model was used to refine the design of the rozanolixizumab FIH study and was subsequently refined itself using the FIH data.[11] To our knowledge, this is the first publication of a semimechanistic PK/PD model that utilized individual PK/IgG clinical data for an anti-FcRn monoclonal antibody-based therapeutic being developed in the clinic, providing an example of good translational science.

Our model is not fully mechanistic and is similar in structure to those described by Kim et al., 2007[13] or Hansen and Balthasar 2003.[24] More complex models, such as PBPK models, were not considered due to knowledge gaps in key parameters at the time of development; for instance, there were limited data on receptor levels across tissues and species. Recent investigations have found differences in FcRn expression across tissues and across species.[25,26] Whole body physiologically-based pharmacokinetic (PBPK) models that provide a more mechanistic description of FcRn biology have been previously described,[27–29] and included aspects, such as pH-dependent binding of IgG to FcRn, tissue-specific FcRn concentrations, and FcRn turnover; in some instances, these models have characterized and predicted the PKs and PDs of IgG antibodies in preclinical species.[24,29–33] Occasionally, these models have been used to characterize human data following mAb administration[33] and have been used to predict the PD effects of i.v. immunoglobulin therapy in humans or to a certain extent anti-FcRn (rozanolixizumab) IgG effects in humans using published mean literature data.[11,32] However, in general, compared with small molecules, the clinical application of PBPK models has been limited until recently.[34] Depending

upon the mechanism of action of the antibody, or whether it elicits TMDD, alternative methodology based on compartmental analysis and semimechanistic modeling using allometric scaling techniques have more frequently been used in translational PK/PD from preclinical to the clinic or across populations, including extrapolation to paediatrics.[1,35–37] These techniques include parameter adjustment to simplify assumptions, based on known interspecies differences for the system under study, and are similar to the methodology used in the current study.

In our model, major assumptions were the estimation of FcRn concentration for the whole body, ignoring dynamic changes, turnover of FcRn, and the endosomal compartment being kinetically indistinguishable from plasma. In comparison, PBPK models apply many fixed assumptions, where FcRn concentration in each tissue is accounted for and similar or different values across species are considered. Cynomolgus monkey data were used to estimate this key parameter of FcRn, characterized as part of the TMDD model when administering different doses of rozanolixizumab and saturating the FcRn receptor to different degrees. The FcRn concentration in cynomolgus monkeys estimated by the model was 0.6 μM (592.89 nmol/L), which was lower than previously published values ranging from 1.6 to 108 μM across mice, rats and humans.[27,33,38,39] However, the actual FcRn concentration determined from cynomolgus monkey liver measured 0.09–0.13 μM (Jairaj, unpublished data), which more closely aligns with the model estimate. Furthermore, the estimated KD in cynomolgus monkeys for the binding affinity of rozanolixizumab for FcRn was 0.827 nM; a value higher than that obtained by SPR[9] but closer to values obtained in MDCK cells expressing cynomolgus monkey FcRn (mean ~ 1 nM at pH 6.0 and pH 7.4).[9]

The PK parameters estimated from the cynomolgus monkey PK study (CLA, V, V2, and Q) were subsequently translated into humans using allometry, where 0.75 was used for clearance-related (CL) parameters. However, although the 0.75 exponent is well-established for small molecules, current literature suggests that higher CL exponents for mAbs (>0.75, usually 0.9) more effectively predict PK from cynomolgus monkeys and interspecies, driven by proteolytic rates across species.[36] The CLA parameter for a typical human subject following allometric translation was 0.76 L/day, representing FcRn-independent elimination of rozanolixizumab. This translated into a rate constant that accounted for the translated human parameters and corresponded to a 0.29 day^{-1} rate of elimination. This aligns with previously reported values for patients with familial hypercatabolic hypoproteinemia lacking the FcRn receptor, where the rate constant was 0.3 per day, with an approximate five-fold increase in the normal catabolic rate of endogenous IgG.[40]

The assumptions for E_{max} and EC_{50} made in our model were validated by observations in preclinical and cynomolgus monkey studies, where the monkey PK/PD data used to develop the model demonstrated 49–75% decreases in IgG from baseline (following the rozanolixizumab dose range studied),[9] that were above the target IgG decrease of 50–60% we believe is required in the clinic. Thus, the assumption of similar maximum rozanolixizumab effect in humans appears reasonable. The estimated turnover rate (K_{out}; endogenous IgG elimination rate constant, which includes full FcRn recycling function) in humans was well aligned with the translated K_{out} (Table 2).

The improved alignment between PK predictions and translated IgG predictions with increasing rozanolixizumab dose could be related to increasing saturation of the FcRn receptor, and the linear component of elimination further driving the PK profile with increasing dose. This was also observed when the PK parameters were re-estimated with the human data,[11] where V, Q, V2, and CLA were aligned with the translated parameters and where those parameters driving nonlinearity differed.

The underprediction of PK for the 1 mg/kg dose level may partly be due to the estimated difference in FcRn concentration eliciting a higher impact for the lower dose. However, there was no cynomolgus monkey data at doses below 5 mg/kg to inform the nonlinear behavior of the system at low concentration range. The continued underprediction of the 1 mg/kg dose in humans by the final model implies some structural component in the model that was unable to account for the higher concentrations observed for the 1 mg/kg dose. However, as the target IgG decrease in the clinic is ~ 50–60% decrease from baseline, it was more relevant for the model to describe data following rozanolixizumab doses of 4 mg/kg and 7 mg/kg. Another potential explanation for the underprediction of the model at the 1 mg/kg dose of rozanolixizumab could be that the excess of IgG relative to rozanolixizumab at this lower dose impedes receptor binding, resulting in a higher concentration-time profile than that predicted by the model. However, rozanolixizumab has a much greater affinity for FcRn, at both neutral and acidic pH (~ 30 pM[9]), compared to 760 nM affinity of IgG for FcRn,[41] only in acidic conditions (i.e., inside the endosome). Thus, rozanolixizumab readily binds to FcRn in plasma, whereas endogenous IgG must undergo pinocytosis before binding to FcRn, therefore even in excess of endogenous IgG it is anticipated that rozanolixizumab would preferentially bind FcRn both in plasma and in the competitive environment of the endosome.

Additionally, in the final PK/PD human model, the estimated E_{max} was lower than the translated E_{max}. This could be driven by the smaller IgG decreases achieved in the human study due to halting rozanolixizumab doses at

7 mg/kg, hence the maximum rozanolixizumab effect on IgG lowering may not have been achieved.[11] At the same time, a lower EC_{50} was estimated in humans compared with the translated EC_{50}, suggesting that a lower concentration would be required to elicit the same effect compared with the initial translated value. Although E_{max} and EC_{50} correlation was not estimated in this study, these parameters have been shown to be correlated,[42,43] therefore the lower EC_{50} may be driven by the lower E_{max} estimate based on the observed data. The PK/PD model in cynomolgus monkeys was able to characterize the system and showed a good predictive performance. As shown in the VPCs (Supplementary Material), the cynomolgus monkey PK/PD model was also able to predict the PK and IgG up to day 12 in the multiple administration data used as external validation. After day 12, the PK is overpredicted by the model and translates in the IgG effect. This overprediction of rozanolixizumab concentrations could theoretically be due to an apparent underlying effect of ADAs that had not yet been detected by the bioanalytical technique, but could already be impacting PKs. However, in the subsequent FIH study, low levels of ADAs were detected but were above the limit of quantification in only five subjects, with no apparent correlation with dose or route of administration.[11]

In the final human PK/PD model, prior distribution was retained for the estimation of some PK parameters (including V2 and Q), because an IgG would be expected to be described by two compartments. Instead of using prior distribution, a potential simplification would have been to use a one-compartment model, as the posterior distribution demonstrated that the human data contributed limited information. For the FcRn concentration parameter, an uninformative prior was applied, and the human data was able to provide information for the estimation. The human data also provided information for KD and aligned it more closely to the higher value for affinity estimated in cynomolgus monkeys (Tables 1 and 2). Additional parameterizations may align more closely with current understanding of FcRn biology rather than the description of an indirect effect of the free drug on IgG elimination, and could include those reflecting the impact of rozanolixizumab on IgG catabolism via inhibition of endogenous IgG recycling, such as: explicit modeling of FcRn changes over time; its ability to bind to either endogenous IgG or rozanolixizumab competitively, with the corresponding respective affinities and within different compartments representing plasma and the endosomal trafficking and cycling; corresponding cycling turnover parameters; and FcRn availability in both plasma and endosome. However, these would have necessitated the addition of several parameters to be estimated (e.g., FcRn turnover, endosomal internalization rate, and turnover of the endosome), leading potentially to overparameterization.

Similarly, the assumption that was made of the free drug driving such an effect on IgG was an approximation. In general, this is appropriate for a cell surface target; in the case of rozanolixizumab, the target is primarily intracellular within endosomes, reached through its clearance pathway. However, the current assumptions were considered to describe the data sufficiently well with the limited data at the time this model was developed, and a more mechanistic description of the process was unnecessary.

In conclusion, the PK/PD model demonstrated good predictive performance both in preclinical stages and with clinical data, and the accuracy for simulations within the dose range of interest was considered important for application during drug development for rozanolixizumab. This work has facilitated the ongoing clinical development of rozanolixizumab for rare autoimmune diseases with high unmet medical needs, including MG and ITP, where the model has been used to select clinically relevant dose regimens in rozanolixizumab clinical trials.[44,45] As more human clinical trial data on rozanolixizumab PK/PD is generated, it is being used to populate and validate the PK/PD model enabling further refinement. The updated PK/PD model and its link to clinical end points will then be used to examine hypotheses related to other aspects of disease and treatment management in future clinical practice.

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CONFLICT OF INTEREST

Rocio Lledo-Garcia, Kate Dixon, Anthony Shock, and Ruth Oliver are employees and stockholders of UCB Pharma.

AUTHOR CONTRIBUTIONS

R.L.-G. wrote the manuscript. R.L.-G., K.D., and R.O. designed the research. R.L.-G. and K.D. performed the research. R.L.-G. and A.S. analyzed the data.

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