Romiplostim dose–response in patients with myelodysplastic syndromes

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Romiplostim, a thrombopoietin receptor agonist approved to treat patients with immune thrombocytopenia (ITP), produces a dose-dependent stimulation of platelet production.
- Following romiplostim dosing in ITP patients, the platelet production is increased by 351% per each 100 µg week⁻¹ in 68% of patients, while the stimulation of platelet production is about 12% per each 100 µg week⁻¹ in the rest of patients.
- Currently, the romiplostim dose–response in patients with myelodysplastic syndromes (MDS) has not been characterized.

WHAT THIS STUDY ADDS

- This study reports a linear dose–response relationship for romiplostim in low or intermediate-1 risk MDS patients.
- At baseline, the platelet production following romiplostim dosing is increased by 269% per each 100 µg week⁻¹ in 78% of patients, while the stimulation of platelet production is negligible in the rest of patients.
- This finding suggests the romiplostim dose–response is similar in MDS and ITP patients.

AIM

To characterize the romiplostim dose–response in subjects with low or intermediate-1 risk myelodysplastic syndromes (MDS) receiving subcutaneous romiplostim.

METHODS

Data from 44 MDS subjects receiving subcutaneous romiplostim (dose range 300–1500 µg week⁻¹) were used to develop a pharmacodynamic model consisting of a romiplostim-sensitive progenitor cell compartment linked to the peripheral blood compartment through four transit compartments representing the maturation in the bone marrow from megakaryocytes to platelets. A kinetics of drug effect model was used to quantify the stimulatory effect of romiplostim on the proliferation of sensitive progenitor cells and pharmacodynamics-mediated disposition was modelled by assuming the kinetics of drug effect constant (k_{DE}) to be proportional to the change in platelet count relative to baseline.

RESULTS

The estimated values (between subject variability) for baseline platelet count, mean transit time, and k_{DE} were $24 \times 10^9 \text{ l}^{-1}$ (47%), 9.6 days (44%) and 0.28 days⁻¹, respectively. MDS subjects had a shorter platelet lifespan (42 h) than healthy subjects (257 h). Romiplostim effect was described for responders (78%) and non-responders (22%). The average weekly stimulatory effect of romiplostim on the production rate of sensitive progenitor cells at baseline was 269% per 100 µg week⁻¹ for responders. Body weight, age, gender and race were not statistically related to romiplostim pharmacodynamic parameters. Visual predictive checks confirmed the model adequacy.

CONCLUSION

The time course of platelet counts in MDS subjects receiving subcutaneous administration of escalating doses of romiplostim was characterized and showed a linear dose–response for romiplostim responders to increase the platelet counts.

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of haematologic malignancies of the pluripotent haematopoietic stem cells characterized by clonal haematopoiesis, progressive bone marrow failure, and the propensity to transform to acute myeloid leukemia (AML) [1, 2]. The incidence of MDS is 3 to 4 cases per 100 000 individuals in the US population, and the prevalence of this disease is expected to continue to increase because therapies for cancer are improving and the population is ageing [3]. Prognosis is estimated by the International Prognostic Scoring System (IPSS) with four risk groups (low, intermediate-1, intermediate-2 and high) for disease progression to AML, and median survival ranges from 5.7 years in patients with low risk MDS to 0.4 years in patients with high risk MDS [4]. Subjects with MDS often present complications related to anaemia (fatigue), neutropenia (infections) and/or thrombocytopenia (bleeding). At the time of diagnosis, 30% of subjects are thrombocytopenic with $\leq 10\%$ initially experiencing serious bleeding. The platelets that are produced in MDS subjects tend to be abnormally large, have poor granulation or large fused central granules, and also decreased aggregation [2]. In addition, MDS subjects have lower *in vivo* platelet activation and *ex vivo* platelet reactivity than subjects with immune thrombocytopenia (ITP) [5]. These data suggest that abnormal platelet function may exist in MDS subjects, making the presence of moderate to severe thrombocytopenia an even greater concern, since the low platelet counts are associated with a poor prognosis and increased risk of AML [6].

The therapeutic options for MDS remain limited. Therefore, supportive care remains an important treatment option for these subjects. Treatments for low and intermediate-1-risk MDS patients include red blood cells and platelet transfusions, recombinant human erythropoietin with or without granulocyte colony-stimulating factors, immunosuppressive therapy, lenalidomide, imatinib or hypomethylating agents [7]. For all MDS risk groups, platelet transfusion for thrombocytopenia is the only treatment option, although its benefit : risk ratio is undesirable.

Romiplostim (Nplate®, AMG 531) is a peptide fusion protein that increases platelet production by binding to the thrombopoietin (TPO) receptor and stimulating megakaryocytopoiesis by the same mechanism as endogenous TPO [8, 9]. Romiplostim is already approved in the US, EU and other countries for treating thrombocytopenia in subjects with chronic immune thrombocytopenia (ITP). Its mechanism of action has made romiplostim an agent of interest as a possible treatment for thrombocytopenia in subjects with low and intermediate-1 risk MDS [7]. The efficacy and safety of romiplostim for the treatment of thrombocytopenic subjects with MDS has been evaluated recently in a clinical trial in which subcutaneous doses ranging from 300 to 1500 μg weekly produced a durable platelet response in 46% of subjects enrolled [10]. In

subjects with low or intermediate risk MDS receiving azacitidine therapy, 750 μg romiplostim administered subcutaneously once weekly significantly raised median platelet counts during cycle 3 on day 1 (450%, $P = 0.0373$) and at the nadir (400%, $P = 0.0035$) compared with placebo [11]. However, romiplostim is not currently indicated for the treatment of MDS.

The pharmacokinetic profile of romiplostim in thrombocytopenic subjects with lower risk MDS indicated that the mean concentration–time profiles after the first dose were higher than those observed after 7 weeks of treatment [10, 12]. This finding is not surprising because binding to TPO receptors on platelets serves as a mechanism for romiplostim clearance, and the platelet counts observed after 7 weeks of treatment were higher than those observed at baseline. This phenomenon has been previously defined as pharmacodynamic-mediated drug disposition (PDMDD) and has been reported for romiplostim [9, 13, 14, 15], but it has not yet been evaluated in MDS subjects. Thus, the main objective of this study was to characterize the romiplostim dose–response in subjects with low or intermediate-1 risk MDS receiving subcutaneous dosing. Secondary objectives were to describe the time course of platelet counts following romiplostim subcutaneous dosing, to quantify the degree of between and within subject variability of romiplostim pharmacodynamic parameters, and to evaluate patient-related covariates as potential sources of variability in the romiplostim dose–response relationship in MDS subjects.

Methods

Clinical data

Data collected from a phase I/II multicentre, open-label, sequential-cohort, dose-escalation study conducted in adult thrombocytopenic subjects with MDS receiving romiplostim were used to conduct this analysis. Eligible adult subjects had confirmed diagnosis of MDS (IPSS low or intermediate-1 risk), a mean baseline platelet count $\leq 50 \times 10^9 \text{ l}^{-1}$, and were only receiving supportive care. The dataset included 1118 platelet counts from 44 subjects receiving 300 μg ($n = 6$), 700 μg ($n = 11$), 1000 μg ($n = 11$) or 1500 μg ($n = 16$) of romiplostim administered subcutaneously once a week for 3 weeks. After evaluation of platelet response at week 4, subjects could continue to receive romiplostim in a treatment extension phase for up to 1 year. In each patient, blood samples were collected at baseline and before the weekly administration of romiplostim, and platelet counts were determined using an automated haematology analyzer. The study was conducted in accordance with principles for human experimentation as defined in the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines and was approved by the respective Investigational Review Boards. Informed consent was obtained from

Figure 1

Schematic of the romiplostim pharmacodynamic model for myelodysplastic syndromes

each subject after they were told of the potential risks and benefits, as well as the investigational nature of the study. Additional details of this clinical trial have been previously reported [10, 12].

Model development

Software Non-linear mixed-effects models using the first order conditional estimation (FOCE) approximation method with INTERACTION option were developed in NONMEM 7.2 (ICON, Ellicott City, MD, USA) [16] using the Intel Fortran XE version 12.0 compiler (Intel Corporation, Santa Clara, CA, USA). Simulations were performed in NONMEM with graphical and statistical analyses undertaken using S-Plus 8.04 (Professional Edition) for Windows (Tibco Software Inc., Palo Alto, CA, USA).

Pharmacostatistical model A modified semi-mechanistic model, originally proposed for neutrophil counts [17] and later expanded for platelet counts in cancer subjects receiving chemotherapy and ITP subjects receiving romiplostim [13, 18], was determined to be a suitable structural model to describe the time course of platelet counts following romiplostim dosing in MDS subjects (Figure 1). The platelet dynamics model consists of six compartments, one representing proliferative cells [Prol] such as stem cells and other progenitor cells, four transit compartments with maturing cells [Transit] and one compartment for circulating platelets [Circ]. A maturation chain with transit compartments and first order rate constants (k_{tr}) allowed for the lag time between romiplostim administration and observed effect on platelet counts. The generation of proliferative cells [Prol] was described as a zero order process quantified by the proliferation rate, k_{prol} . The model differential equations are shown below:

$$\frac{dProl}{dt} = k_{prol} \times E_{Drug} - k_{tr} \times Prol \quad (1)$$

$$\frac{dTransit_1}{dt} = k_{tr} \times Prol - k_{tr} \times Transit_1 \quad (2)$$

$$\frac{dTransit_N}{dt} = k_{tr} \times Transit_{N-1} - k_{tr} \times Transit_N; \quad (3)$$

for $N = 2, 3$ and 4 .

$$\frac{dCirc}{dt} = k_{tr} \times Transit_4 - k_{circ} \times Circ \quad (4)$$

The model assumed that the only loss of cells in the transit compartments was to the next compartment. Therefore, the random loss of precursor cells was assumed to be negligible, allowing the estimated mean transit time (MTT) to become apparent. As the proliferative cells differentiate into more mature cell types, the number of cells was maintained by cell division. Before administering romiplostim, the biological system was assumed to be at steady-state and, therefore, $dProl/dt$ was equal to 0 and, therefore, $k_{prol} = k_{tr} \times Prol_0 = k_{circ} \times Circ_0$, where $Prol_0$ and $Circ_0$ were the proliferative cells and platelet counts at baseline, respectively. To improve interpretability, the MTT was estimated based on the number of transit compartments (N) as follows:

$$MTT = \frac{N+1}{k_{tr}} \quad (5)$$

To simplify the complex pharmacokinetics of romiplostim, a ‘kinetics of drug action’ (K-PD) model [13, 19–21] was used to relate romiplostim dosing to platelet count. A virtual dose-driving rate (DODR) was used to characterize the stimulatory effect of romiplostim on k_{prol} according to linear stimulatory function:

$$E_{\text{Drug}} = 1 + \alpha \times \text{DODR} = 1 + \alpha \times k_{\text{DE}}(t) \times A(t) \quad (6)$$

where α represented the stimulatory effect of romiplostim, $k_{\text{DE}}(t)$ was the first order equilibration rate of the virtual compartment, and $A(t)$ was the amount in the virtual compartment. Based on the romiplostim PDMDD previously described [14], $k_{\text{DE}}(t)$ was assumed to be proportional to the relative change in platelet counts from baseline. Thus, the differential equation describing the kinetics of the virtual compartment driving the drug effect was defined as:

$$\frac{dA}{dt} = -k_{\text{DE}}(t) \times A = -k_{\text{DE}}^0 \times \frac{\text{Circ}}{\text{Circ}_0} \times A(t) \quad (7)$$

where k_{DE}^0 was the first order equilibration rate of the virtual compartment at baseline. Thus, the system-related parameters estimated were Circ_0 and MTT , while the drug-specific parameters were k_{DE}^0 and α . Because the graphical exploration of the individual fits and model parameters suggested that the response to romiplostim dosing was variable across subjects, a mixture of models accounting for the difference in response across subjects was implemented. For the subpopulation of subjects whose platelet time course corresponded to their romiplostim dosing (Population 1), the parameters of the model were determined. In the other subpopulation (Population 2), the predicted platelet count was set to the estimated baseline platelet count, which is equivalent to assume $\alpha = 0$.

Between- and within-subject variability (IIV and IOV) in the model parameters were assumed to follow a log-normal distribution. However, since Circ_0 was not normally distributed, a Box-Cox transformation was used and a shape parameter was estimated to describe this distribution. For subjects who received multiple doses of romiplostim, occasions were arbitrarily defined every 6 weeks (initial treatment duration) for up to four occasions. After the logtransformation at both sides, residual variability (RV) was described using an additive plus proportional error model for Population 1 and an additive error for Population 2 after the log-transformation at both sides.

The effect of age, weight and gender on the romiplostim pharmacodynamic parameters was explored graphically and evaluated following the forward-inclusion ($P < 0.005$) and backward-elimination ($P < 0.001$) processes previously described [22]. The effects of continuous covariates were modeled multiplicatively using normalized power models, while the effects of categorical covariates were modelled multiplicatively using a similar notation:

$$\text{TVP} = \theta_n \times \prod_{m=1}^M \left(\frac{\text{COV}_m}{\text{ref}_m} \right)^{\theta_{(n+m)}} \times \prod_{p=1}^P \theta_{(n+M+p)}^{\text{COV}_{M+p}} \quad (8)$$

where the typical value of a model parameter (TVP) was described as a function of M individual continuous covariates (cov_m , $m = 1, \dots, M$) and P individual categorical (0 or 1) covariates (cov_{M+p} , $P = 1, \dots, P$). θ_n is the estimated typical model parameter value with covariates equal to the reference covariate values ($\text{cov}_m = \text{ref}_m$, $\text{cov}_{M+p} = 0$). $\theta_{(n+m)}$ and $\theta_{(n+M+p)}$ are the estimated parameters that describe the magnitude of the covariate-parameter relationships. In addition, if the magnitude of the model parameter change due to a covariate's influence was less than 20% over the range of values evaluated, the covariate factor was not considered to be clinically relevant and, consequently, was not incorporated into the model.

Model selection criteria Models that converged successfully with estimation of asymptotic standard errors, produced reasonable parameter estimates, and had low IIV, IOV as well as low RV were preferred. The minimum value of the objective function (MVOF), a statistic that is proportional to minus twice the log-likelihood of the data, was used to calculate the likelihood ratio test. For hierarchical models, the likelihood ratio test is the difference in MVOF between two models, and represents a statistic that is asymptotically χ^2 distributed, with degrees of freedom (d.f.) equal to the number of parameters added to or deleted from the model. A change in the MVOF of ≥ 7.88 was required during model development, which represented a statistical significance ($\alpha = 0.005$) for the addition of one fixed effect to the model. An apparently conservative P value was selected to avoid the inclusion of weak and clinically non-relevant effects and to control for multiple testing. With this methodology, only covariates showing significant contributions were kept in the pre-final population model. Standard diagnostic plots of goodness-of-fit and the shrinkage for the Empirical Bayesian Estimates (EBE) of the IIV and IOV [23] were also used to evaluate models. The distribution of the interindividual random effects and the correlation between them were examined graphically to evaluate the normality and the independence assumption, respectively. The random effects with the highest correlation were tested by including the corresponding non-diagonal elements in the matrix of random effects.

Model evaluation An internal visual predictive check (VPC) [24] stratified by dose was conducted to provide visual comparison between distributions of simulated platelet counts to those observed in the analysis datasets. In this visual check, the platelet count time profiles were simulated using the final model parameters and the 80% prediction intervals were generated to compare the observed and simulated distributions. In addition, model evaluation was also conducted by assessing the normalized prediction distribution error (NPDE) [23].

Results

Baseline characteristics of the study population are summarized in Table 1. A model previously developed for describing the time course of platelet counts after subcutaneous romiplostim administration in ITP subjects [13] was empirically modified to account for the PDMDD of romiplostim and proved to provide a reasonable description of the data analyzed in the present study. Figure 2 displays the standard diagnostic plots showing the model goodness-of-fit for platelet counts, which did not suggest any model mis-specification. The observed vs. model-predicted plots (upper panels) showed a normal random scatter around the identity line and indicated the absence of significant bias or model misfit. Similarly, the distribution of conditional weighted residual (middle panels) [25] and NPDE (lower panels) as a function of the population predictions (left panels) and time (right panels) did not show any trend that suggested model inadequacy. The mean and SD of the NPDE for platelet counts confirmed the model accuracy and precision, because the mean and SD of the NPDE were very close to 0 and 1, respectively.

Table 1

Summary of subjects' demographics at baseline

Characteristic	Analysis dataset (n = 44)
Mean age (years) (range)	74 (31–94)
Mean weight (kg) (range)	76.7 (47–122)
Gender, n (%)	
Male	32 (72.7)
Female	12 (27.3)
Race, n (%)	
White	39 (88.6)
Black	1 (2.4)
Hispanic	2 (4.5)
Asian	2 (4.5)

Table 2

Final parameter estimates of the romiplostim pharmacodynamic model for MDS subjects

Parameter (Units)	Population estimate [RSE (%)]	Inter-individual variability [RSE (%)]	Shrinkage (%)
k_{DE}^0 (days ⁻¹)	0.16 (2.61)	–	–
k_{Circ} (days ⁻¹)	0.57 (10.9)	36.3 (70.9)	30.9
$Circ_0$ ($\times 10^9$ l ⁻¹)*	23.7 (9.83)	47.0 (29.7)	12.4
MTT (days)	9.58 (11.5)	44.7 (25.8)	13.2
Effect			
Subpopulation 1, %	77.7 (33.3)	–	–
α (day/ μ g)	0.28 (4.07)	163 (44.6)	12.1

$Circ_0$, baseline platelet count; Effect, romiplostim effect; k_{Circ} , Elimination rate constant for platelet count; k_{DE}^0 , Elimination rate constant for dose; MTT, mean transit time; RSE, relative standard error; subpopulation 1, individuals with platelet response to romiplostim dosing. *Shape parameter for Box-Cox transformation (RSE) was –0.23 (50.0%). Interoccasion variability (RSE) of Effect was 84.9% (18.3%) and the associated shrinkage was 12.2. Residual variability (RSE) for subpopulation 1 was 20.4% (3.83%) for the proportional error term and 0.69×10^9 l⁻¹ (6.6%) for the additive error term. Residual variability (RSE) for subpopulation 2 was 1.59×10^9 l⁻¹ (7.11%) for the additive error term.

The final model parameter estimates are presented in Table 2. For system-related parameters, both fixed and random effects were estimated with relatively good precision, except the shape of the Box-Cox transformation for $Circ_0$ and the IIV of k_{Circ} , which were acceptable. The system-related parameter estimates indicate that MDS is a disease characterized by rates of production and destruction of platelets that are different from those of healthy subjects. The production rate of progenitor cells and platelet lifespan were estimated to be 0.52×10^9 cells l⁻¹ h⁻¹ and 42 h, respectively. Romiplostim response was described for two MDS subpopulations: responders (78%) and non-responders (22%). Including a mixture of models (i.e. for responders and non-responders) resulted in a reduction in the objective function (Δ MOFV –28). The typical weekly average romiplostim stimulatory effect on progenitor cells at baseline was estimated to be 269% after 100 μ g week⁻¹ in the MDS responder subpopulation. Attempts to estimate more complex drug effect models for responders, including an E_{max} model, failed. The shrinkage estimates were lower than 0.31 for inter-individual random effects. The inclusion of IOV in the model reduced the MVOF by more than 200 points and, as expected, there was a significant reduction in the residual variability and the IIV in the drug effect parameters. Among the responders, the proportional error term of the residual variability decreased from 25% to 20% and the additive error term decreased from 0.80 to 0.69×10^9 l⁻¹. Furthermore, the interindividual variability in the drug effect was reduced from 187% to 163%. The likelihood ratio test suggested that age, body weight, gender and race had no discernable effect on $Circ_0$, k_{Circ} , MTT or α .

Figure 3 displays the individual observations and model predictions for randomly selected subjects responding to romiplostim. In this plot, the initial response to romiplostim is evidenced by an increase in platelet counts a few days after the start of treatment. The peak platelet counts achieved within the first months of treatment are followed by a slight systematic decline in platelet

Figure 2

Standard diagnostic plots of the final model

counts in the absence of any romiplostim dose reduction. This phenomenon is due to the romiplostim PDMDD, which resulted in non-stationary platelet counts that can be handled empirically by making k_{DE} proportional to the relative change in platelet counts from baseline.

The results of the VPC on the platelet counts time course for subjects in the responder subpopulation are displayed in Figure 4. Plots for each dose group, showing the 10th, 50th and 90th prediction intervals for platelet counts were overlaid with the observed data, and approximately 80% of the observed platelet count data fell between the 10th and 90th prediction intervals for each dose group, which was indicative that the model could properly capture the variability of the observed data.

Observations outside the prediction interval were approximately evenly distributed above and below the interval. Taken together, the results of the VPC and NPDE, used as complementary methods to assess the validity of the model, evidenced the adequacy of the model to predict the time course of platelet count, and the overall model performance was judged to be acceptable.

Discussion

A semi-mechanistic pharmacodynamic model developed previously for ITP patients receiving subcutaneous romiplostim was adapted to describe the time course of

Figure 3

Individual platelet counts and model predictions for subjects responding to romiplostim dosing. Circles represent observed platelet counts, line represents individual model prediction and diamonds represent romiplostim administrations

platelet counts in subjects with low or intermediate-1 risk MDS receiving subcutaneous romiplostim doses. The model shares many similarities with the semi-mechanistic pharmacodynamic model previously developed for describing the stimulatory effect of romiplostim in platelet production in ITP patients [13], but also has some important differences. For example, the current model included a term describing k_{DE} as a function of platelet count relative change from baseline to account for the PDMDD phenomenon previously described, individual response to the romiplostim stimulatory effect was separated into populations of responders and non-responders, a Box-Cox transformation was used to normalize the distribution of $Circ_0$, and k_{circ} was estimated from the data instead of fixing at the k_{tr} value.

Several methods for analyzing dose–response time data in the absence of pharmacokinetic data have been previously suggested [26]. These methods are also necessary or convenient to simplify the pharmacokinetic information and conduct longitudinal dose–response analysis. As happened in the romiplostim model for ITP patients, in

this study the complexity of the pharmacokinetic model of romiplostim and the limited pharmacokinetic and pharmacodynamic data available justify the use of the K-PD approach [19, 21]. K-PD models involving extravascular dosing have previously used an additional hypothetical pharmacokinetic compartment to shift the time to peak amount of drug at the biophase. However, it was not possible in this case because there is no information available within a dosing interval to identify properly the parameters that quantify the delay distribution to biophase. This identifiability issue is a consequence of the sampling times scheduled for platelet counts relative to the dosing interval, t_{max} and platelet lifespan. In fact, platelets counts were measured just before the weekly administration of romiplostim. However, the romiplostim time to achieve peak serum concentrations after dosing and the average platelet lifespan is shorter than 2 days.

Although the K-PD model used in this study involves a simplification of the complex pharmacokinetic processes following administration of romiplostim, the model was developed on the basis of only one type of observation

Figure 4

Visual predictive check for the time course of platelet counts stratified by the romiplostim dose. Circles represent observed platelet counts and lines represent the 10th, 50th and 90th prediction intervals for platelet counts

(platelet count). It described the data adequately and incorporated many important structural features of the haematopoietic system, such as cell production, maturation and degradation, as well as the stimulatory effect of romiplostim on the production rate of progenitor cells and the romiplostim PDMDD. As romiplostim is bound to TPO receptors and its pharmacological action leads to an increase in platelet count that results in a time-dependent change in the total number of receptors, the pharmacokinetics of romiplostim are time-dependent (non-stationary), as has been demonstrated for other recombinant haematopoietic growth factors [27–29]. In the context of the K-PD approach, the romiplostim PDMDD was mathematically accounted for by empirically setting k_{DE} to be directly proportional to the relative change in platelet count from baseline (equation 7). This approach was proven useful to describe the non-stationary time course of platelet count at the individual level (Figure 3). In general, platelet counts rise rapidly a few days after treatment initiation and reach a peak after approximately 2.5 weeks following weekly dosing of romiplostim. The initial increase in platelet count following administration of romiplostim followed by a subsequent decline in platelet count was due to the romiplostim PDMDD, which helped maintain platelet count homeostasis. Therefore, increasing the platelet count results in increased clearance and k_{DE} , which in turn reduce the peak pharmacodynamic effect of romiplostim in the absence of a dose reduction.

In healthy subjects, the lifespan of platelet precursors and platelets were modelled using 10 transit compartments [14]. Transit compartment models are a special case of lifespan indirect response models with the lifespan distribution described by a gamma function. If the drug affects only the production of precursor cells, as romiplostim does, then an increase in the number of transit compartments results in a lifespan indirect response model with a time-invariant point lifespan distribution. This model can be approximated by a transit compartment model when the number of compartments is at least five [30, 31]. Therefore, the romiplostim PK-PD model for healthy subjects was simplified to have only five compartments (one proliferative compartment and four ageing compartments) describing the dynamics of platelet precursors in both ITP [13] and MDS populations. The reduction in the number of transit compartments to describe the lifespan of platelets in MDS is due to the reduction in the lifespan of platelets in MDS relative to healthy subjects. Since in this target population the platelet lifespan is less than 2 days, one compartment was sufficient to describe the platelet counts time course as happened in the ITP population [13].

The production rate of progenitor cells and platelet lifespan were estimated to be $0.52 \times 10^9 \text{ cells l}^{-1} \text{ h}^{-1}$ and 42 h, respectively, which are both significantly smaller than estimates of $0.87 \times 10^9 \text{ cells l}^{-1} \text{ h}^{-1}$ and 257 h determined for healthy subjects, but similar to the estimates determined in ITP subjects, $0.30 \times 10^9 \text{ cell l}^{-1} \text{ h}^{-1}$ and 34 h [13, 14].

In addition, the mean transit time from progenitor cells to platelets was estimated to be 142 h and 170 h in healthy subjects and ITP patients, respectively, which are both significantly lower than the value obtained in this analysis for MDS subjects (230 h). However, the sum of the lifespan of platelets and precursor cells in MDS subjects (272 h) is shorter than the estimated value in healthy subjects (395 h), and similar to the value estimated for ITP patients (204 h) [14].

Similar to the findings in ITP subjects, the response to romiplostim in MDS subjects was highly variable, which justifies the need for dose titration to maintain the platelet count within the target range. Moreover, approximately 78% of MDS subjects exhibited a platelet response consistent with the romiplostim dose received while the remaining 22% of subjects did not exhibit any relationship between romiplostim dose and platelet response. The physiological mechanism associated with the lack of response in certain patients is not well known and requires further investigation. In the responder subpopulation, the stimulatory effect of romiplostim was found to be very robust despite the large IIV and IOV. Actually, at baseline, the platelet production increased, on average, 269% for each 100 µg week⁻¹. Part of the unexplained residual variability could be due to the variability in pharmacokinetics, which could not be explored using the K-PD model developed in the present analysis. Since no effects of covariates on model parameters were identified, there is no direct impact on the initial dose recommendation for future clinical studies. Subsequent dose adjustments are based on platelet counts, which indirectly account for the patient sensitivity to the romiplostim dosing regimen administered.

The negative feedback process relating circulating cells to the production rate of progenitor cells included in previous pharmacodynamic models for neutrophil counts [17] was not included in the present model due to theories suggesting that TPO is constitutively produced and that TPO expression cannot be induced [32].

In summary, a semi-mechanistic pharmacodynamic model was developed to describe the time course of platelet counts in subjects with low or intermediate-1 risk MDS receiving subcutaneous romiplostim at clinically relevant doses. The model accounted for the romiplostim PDMDD in MDS subjects, who had shorter platelet lifespan and lower rates of progenitor cell production and maturation than healthy subjects, with no significant effects of age, weight or gender on model parameters. This model allowed characterization of a linear dose–response relationship for romiplostim in low or intermediate-1 risk MDS patients for the first time. At baseline, the platelet production following romiplostim dosing increased by 269% per each 100 µg week⁻¹ in 78% of patients, while the stimulation of platelet production was negligible in the rest of patients. This finding suggests the romiplostim dose–response is similar in MDS and ITP patients.

Competing Interests

All authors have completed the Unified Competing Interest form http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare this study was funded by Amgen, Inc.. J.J. Perez-Ruixó, S. Doshi, and Y.M.C. Wang were employees at Amgen, Inc. at the time this analysis was conducted. D.R. Mould was a consultant for Amgen, Inc., and received consultation fees for this project. There are no other relationships or activities that could appear to have influenced the submitted work.

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