Semi-Physiological Population PK/PD Modeling of Eltrombopag in Healthy Volunteers and Patients with Idiopathic Thrombocytopenic Purpura

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Introduction

Eltrombopag is an orally bioavailable, small molecule, non-peptide thrombopoietin receptor (TPO-R) agonist that has been recently approved in the United States for treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP). The population pharmacokinetics (PK) of eltrombopag in healthy volunteers and patients with ITP have been described previously[1]. The model identified health status (healthy volunteer (HV) vs. ITP patient), weight, East Asian race, concomitant use of corticosteroids, gender and dose (≤ 20 mg) as predictors of eltrombopag exposure.

Objectives

➢To develop a semi-physiological model describing the relationship between plasma eltrombopag and platelet counts (PLTC) in healthy volunteers and patients with ITP.

➢To identify predictors of pharmacodynamic (PD) response.

Methods

Model Development

- PD data were fitted alone using individual posthoc PK parameter estimates from the population PK model[1] to compute eltrombopag concentrations in NONMEM.
- Population PK/PD analyses were performed sequentially, first for healthy volunteers and then for patients with ITP.
- Explore predictors of PD response
  - Demographic predictors of PK (race, gender and weight)
  - Age and baseline platelet count (HV)
  - Age, concurrent use of corticosteroids, prior use of ITP medications, splenectomy, and baseline thrombopoietin (patients with ITP).

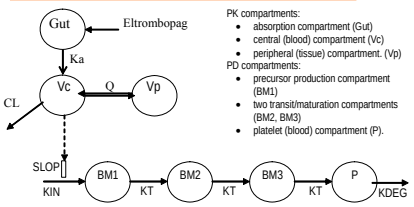
Model Evaluation

- Visual predictive checks (VPC) (overall and stratified by dose and by study for healthy volunteers).
- Nonparametric bootstrap analysis stratified by gender in healthy volunteers only (long run times).

Model Description

- A life-span[2] PK/PD model was implemented with 3 PK and 4 PD compartments (Fig 1).
- Stimulation of PLTC production by eltrombopag was achieved through increase in the zero order production rate of platelet precursors (KIN); KIN increased linearly with eltrombopag concentration (SLOP).
- A mixture model was introduced to account for non-responders in patients with ITP.
- The natural life-span of platelets as well the platelet response to eltrombopag was expected to differ between patients with ITP and HV. Differences in platelet degradation rate (KDEG) between the 2 populations were introduced indirectly through PLTC at baseline (KDEG=KIN/BASE).
- KIN and KT (rate of production & maturation) assumed to be the same in HV and patients. This is largely in agreement with the disease etiology[3] of ITP that the rapid degradation of platelets is the major contributor to thrombocytopenia in patients with ITP. In addition, the sparse and/or variable nature of the PLTC data for patients with ITP was not sufficient to independently estimate KINand KT.

Figure 1. Schematic Representation of the PK/PD Model



PK compartments:
- absorption compartment (Gut)
- central (blood) compartment (Vc)
- peripheral (tissue) compartment. (Vp)

PD compartments:
- precursor production compartment (BM1)
- two transit/maturation compartments (BM2, BM3)
- platelet (blood) compartment (P).

CL: Clearance, Ka: first order absorption rate constant, Vc = volume of central compartment, Q: inter-compartmental clearance, Vp = volume of peripheral compartment, KIN: zero-order production rate of platelet precursors, KT: first-order maturation rate of platelet precursors, KDEG: first-order platelet degradation rate, SLOP: linear proportionality constant of drug effect

Data

	Data in HV	Data in ITP Patients
N	111 subjects	88 patients on eltrombopag 67 patients on placebo
Studies	3 Phase 1	1 Phase 2 & 1 Phase 3
Dose and Duration	Single and Repeat Doses 5-200 mg QD up to 10 days	Repeat Doses 0, 30, 50 and 75 mg QD for 6 weeks
Number of platelet measurements	1728 (baseline, Day 1 and up to Day 28, Follow Up)	627 (eltrombopag) and 590 (placebo) measured weekly
Baseline Platelet Count (Gi/L)	217 (121-393) Baseline is 45 Gi/L higher in women on average than in men	16 (1-40)* Baseline is 8 Gi/L higher in East Asian on average than in Caucasians/ Others
Covariates	13% Female	65% Female * 31% Use of corticosteroids 75% Prior ITP medications 43% Splenectomy Baseline thrombopoietin 26-200 ng/L

Summary for baseline and all covariates in patients receiving eltrombopag only

Results

Healthy Volunteer Results (Table 1):
- 32% increase in KIN for each 1 µg/mL of eltrombopag.
- Blood platelet half-life of 105 hr.
- Females were less sensitive to eltrombopag (36% lower SLOP).
- PLTC were higher in East Asian race and in females because of greater exposure to eltrombopag (Fig 2).
- VPC: 5.7% of the observed PLTC fell outside the 90% PI.
- NONMEM and bootstrap estimates were almost identical and CI were very close for all the parameters.

ITP Patient Results (Table 1):
- PLTC did not change over time in patients receiving placebo.
- 81% responded to eltrombopag (P1) with a 58% increase in KIN for each 1 µg/mL of eltrombopag; non-responders (19%) had SLOP=0.
- Blood platelet half-life of 8 hr.
- Females were more sensitive to eltrombopag (2.4-fold higher SLOP than males) as well as older patients (SLOP ranged from 0.158 to 1.14 mL/µg in male ITP patients of 18 to 85 years old).
- PLTC were higher in East Asian race > (Age ≥65 years) > (baseline >15 Gi/L) > Females > Corticosteroid use either because of greater PD response or greater exposure to eltrombopag (Fig 3).
- VPC: overall 4.8% of the observed PLTC fell outside the 90% PI.

Overall:
- Diagnostic plots (Fig 4) indicated that the final models adequately described the data.
- The opposing results in the influence of gender on SLOP may be due to differences in the disease between males and females or due to the relatively small numbers of female HV (n=14 out of 111) compared to female patients (n=57 out of 88).
- The identification of the age effect in ITP patients may have been due to the wide range of ages enrolled in the ITP patient studies (18 to 85 years); whereas, the range of ages enrolled in the HV studies was more limited (18 to 49 years).

Table 1. Parameter Estimates of Eltrombopag Population PK/PD Healthy Volunteer and ITP Patient Models

Parameter [Units]	Healthy Volunteer Final Model Estimate (95% CI)	%RSE	ITP Patient Final Model Estimate (95% CI)	%RSE
SLOP [mL/µg]	0.323 (0.274, 0.372)	7.80	0.579 (0.340-0.818)	21.1
KIN [Gi/L.hr]	1.43 (1.07, 1.79)	12.8	1.43 FIXED	
KT [hr^{-1}]	0.0253 (0.0221, 0.0285)	6.36	0.0253 FIXED	
P(1)	-		0.811 (0.714-0.908)	6.09
SLOP ~ SEX	0.644 (0.448, 0.840)	15.5	2.42 (1.15-3.69)	26.9
SLOP~AGE	-	-	1.27 (0.525-2.01)	29.9
Inter-individual variability				
ω^2_{SLOP}	0.313 (0.113, 0.513)	32.6	0.804 (0.343-1.26)	29.2
Covar ω_{CL}, ω_{KT}	-0.259 (-0.435, -0.0834)	34.6	-	-
ω^2_{KIN}	0.762 (0.354, 1.17)	27.3	0 FIXED	-
ω^2_{KT}	0.161 (0.0806, 0.241)	25.5	0.573 (0.359-0.787)	19.0
ω^2_{BASE}	0.00535 (0.00344, 0.00726)	18.2	0.0873 (0.0275-0.147)	34.9
Residual variability				
σ_{prop}	0.0453 (0.0155, 0.0751)	33.6	0.446 (0.375-0.517)	8.07
σ_{add}	11.2 (4.18, 18.2)	32.0	2.96 (1.72-4.20)	21.4

Abbreviations: KIN: zero order production rate of platelet precursors; KT: first order maturation rate of platelet precursors; SLOP: linear proportionality constant of drug effect; P1: proportion of patients responding to drug; %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; σ^2_{prop} = proportional component of the residual error model; σ^2_{add} = additive component of the residual error model; SD=standard deviation of additive error ($=\sqrt{\sigma^2_{add}}$)

The healthy volunteer reference population for PD parameter SLOP is males. SLOP~SEX: $0.323^{0.644 \text{ male}}$ [SEX: Male=0, Female=1].

The ITP patient reference population for PD parameter SLOP is 50 year old male responder. SLOP~SEX: $0.579^{2.42 \text{ men}}$ [SEX: Male=0, Female=1]. SLOP~AGE: $0.579^{[AGE/50]^{1.27}}$.

KIN and KT for patients with ITP fixed based on estimates from Healthy Volunteer model

Figure 2. Simulated Median PLTC vs Time by Gender and Race for Eltrombopag 50 mg QD x 10 days in HV

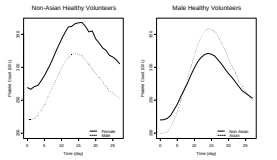


Figure 3. Simulated Median PLTC vs Time by Gender, Race, Corticosteroid Use, Age, Baseline and Responder Status for Eltrombopag 50 mg QD x 6 weeks in ITP Patients

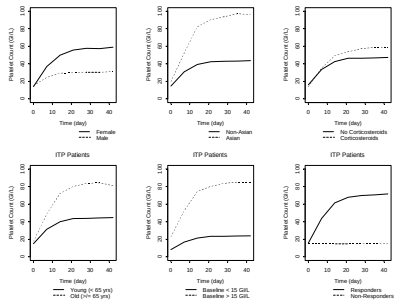
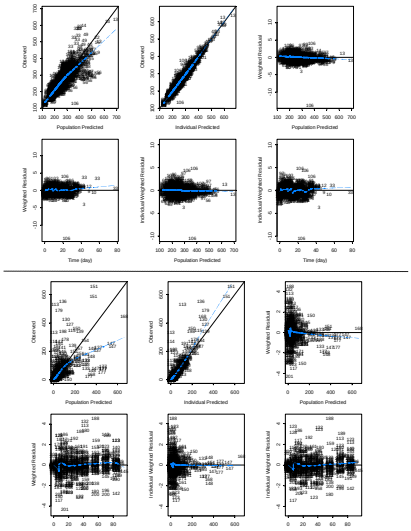


Figure 4. Diagnostic Plots for HV (Top) and Patients with ITP (Bottom)



Conclusions

The developed semi-physiological population PK/PD model adequately described the relationships between plasma eltrombopag concentrations and PLTC in healthy volunteers and patients with ITP and identified patient characteristics predictive of the effects of eltrombopag on platelet response.

References

[1] E. Gibiansky, J. Zhang, D. Williams, Z. Wang, D. Ouellet. Population Pharmacokinetics of Eltrombopag in Healthy Subjects and Patients with Chronic Idiopathic Thrombocytopenic Purpura. PAGE 18 (2009) Abstr 1502 [www.page-meeting.org/?abstract=1502].

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