Population Pharmacokinetics of Eltrombopag in Patients with Cancer and Healthy Subjects

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BACKGROUND

- Eltrombopag is an oral once-daily nonpeptide thrombopoietin receptor (TPO-R) agonist;
- Approved in US for patients with chronic idiopathic thrombocytopenic purpura (ITP);
- In development for chemotherapy induced thrombocytopenia (CIT);
- The population pharmacokinetics (PK) of eltrombopag in patients with ITP and healthy subjects (HV) have been described previously [1].

OBJECTIVES

- To develop a population PK model of eltrombopag in patients with cancer;
- To identify demographic/covariate factors influencing eltrombopag exposure and quantify relative impact of these covariates in patients with cancer.

DATA

3991 eltrombopag concentrations from 163 healthy subjects (rich sampling):

- 18-50 years; 49-99 kg; 23% females; 4% East Asians, 13% African-Americans; 34% administered capsules
- 5-200 mg, administered as a single dose and/or QD for 5-10 days

753 eltrombopag concentrations from 125 patients with advanced solid cancers receiving paclitaxel/carboplatin (mix of sparse and serial PK sampling):

- 33-81 years; 30-111 kg; 51% females; 8% East Asian, 100% administered tablets
- 50, 75 or 100 mg eltrombopag once-daily (QD) on days 2-11 of each 21-day cycle.

METHODS

- Mixed-effects modeling approach; first-order conditional method (FOCEI) of NONMEM VI;
- The population PK model [1] developed for healthy volunteers and ITP patients was used; covariate relationship were investigated in the new population.

METHODS

Model [1] (in ITP patients and HV) included:

- 2-compartment linear model; dual sequential first-order absorption with lag time and inter occasion variability; higher residual variability during absorption phase and for patients;
- Increase of CL/F, Q/F, Vc/F, and Vp/F with weight, decrease of CL in ITP patients, Asians, females, and with concomitant use of corticosteroids.
- PK of low sub-therapeutic doses (< 20 mg) differed from higher doses, and was accounted for in the model by including separate estimates for CL/F and Vc/F.

Covariate modeling methodology

- The full model approach was implemented: all *apriori* chosen covariate-parameter relationships of interest were entered in the model simultaneously; parameters were estimated; covariates with precisely estimated and negligible effect and poorly estimated covariates (based on confidence intervals of parameter estimates) were excluded from the model;
- The full model did not simultaneously include highly correlated covariates; therefore several full models (with one of the competing correlated covariates) were investigated;
- Covariates were selected based on the representation (>10% of HV or patients); covariate's range and correlation; scientific interest (including all covariates predictive of ITP PK), mechanistic plausibility, and exploratory graphics.
- Covariates modeled multiplicatively as power functions.

Model evaluation

- Diagnostic plots (DV vs PRED, IPRED; WRES, IWRES vs PRED, TIME, TAD; distributions and correlations of random effects, overall and stratified by population);
- Visual predictive check simulations (VPC), overall and stratified by dose and study

Table 1

Parameter	Estimate	%RSE	95% CI
CL/F [L/hr]	0.839	3.93	0.774-0.904
Vc/F [L]	11.7	6.44	10.2-13.2
Vp/F [L]	9.81	10.3	7.83-11.8
Q/F [L/hr]	0.546	3.79	0.505-0.587
KA1 [1/hr]	0.386	6.53	0.337-0.435
KA2 [1/hr]	4.03	11.2	3.15-4.91
ALAG1 [hr]	0.453	1.86	0.437-0.469
MTIME [hr]	1.45	1.20	1.42-1.48
σ_{Prop} ~Cancer	1.54	7.27	1.32-1.76
σ_{Prop} ~TAD<4hr	1.23	3.85	1.14-1.32
CL/F ~DOSE<20 mg	1.67	6.41	1.46-1.88
Vc/F ~DOSE<20 mg	1.61	6.07	1.42-1.80
Vp/F ~DOSE<20 mg	0.312	29.6	0.131-0.493
Vc/F ~Healthy	0.742	6.73	0.644-0.840
CL/F ~Asian	0.525	11.1	0.410-0.640
Vc/F ~Asian	0.660	8.30	0.553-0.767
CL/F ~Female	0.845	5.55	0.753-0.937
CL/F ~Age	-1.17	22.1	-1.68- -0.664

Variability	Estimate	%RSE	95% CI	CV% or R
ω^2_{CL}	0.197	11.5	0.153-0.241	CV= 44.4%
Covar ω_{CL}, ω_{Vc}	0.131	14.8	0.0930-0.169	R= 0.765
ω^2_{Vc}	0.149	15.9	0.103-0.195	CV= 38.6%
$\omega^2_{IOV\ Ka1}$	1.44	7.50	1.23-1.65	CV= 120%

Residual variability	Estimate	%RSE	95% CI	CV% or SD
σ^2_{prop}	0.0420	7.64	0.0357-0.0483	CV= 20.5%
σ^2_{add}	520	41.3	98.6-941	SD=22.8

SE: standard error , %RSE: percent relative SE of the estimate = SE/parameter estimate *100; CL/F = apparent clearance, Vc/F = volume of central compartment, Ka1 = absorption rate constant prior to MTIME, Ka2 = absorption rate constant after MTIME, Q/F = inter-compartmental exchange flow rate, Vp/F = volume of peripheral compartment, ALAG1 = lag-time, σ^2_{prop} = proportional component of the residual error model, σ^2_{add} = additive component of the residual error model, σ_{Prop}~Cancer = factor of proportional error for patients with cancer; σ_{Prop}~TAD<4hr = factor of proportional error for TAD < 4 hours (absorption time); CI= confidence interval on the parameter; R= correlation coefficient; ω^2_{CL} and ω^2_{Vc} = covariance of random effect of CL/F and Vc/F, respectively; Covar ω_{CL}, ω_{Vc} = correlation between covariances of random effect of CL/F and Vc/F; ω^2_{IOV} Ka1 = covariance of random effect of IOV on Ka1; SD=standard deviation of additive error (=$[\sigma^2_{add}]^{0.5}$), R= correlation coefficient. The reference population for CL/F and Vc/F are 50 years Caucasian males with cancer.

RESULTS

- Structural and absorption model [1] was adequate for the new population;
- Model parameter estimates are presented in Table 1;
- All model parameters were independent of weight;
- Apparent clearance (CL/F):
  - Decreased with AGE for patients >50 years old (43% lower at 81 years relative to <50 year-old patients)
  - 47% lower in Asians compared to all other races;
  - 15% lower in females compared to males;
- Apparent Volume (Vc/F):
  - 34% lower in Asians compared to all other races
  - 26% lower in HV relative to patients with cancer.
- At low (<20 mg) doses, CL/F was 67% higher, Vc/F was 61% higher, Vp/F was 69% lower;
- No influence of moderate renal impairment (based on 11 patients);
- No influence of smoking (based on 55 smokers, despite being a CYP1A2 substrate).
- Graphical diagnostics did not show any deficiencies;
- VPC: no bias; approximately 90% of observations were within 90% prediction intervals for each of doses and studies

CONCLUSIONS

- The model adequately described eltrombopag PK in patients with cancer and healthy subjects.
- CL/F in patients with cancer and HV was higher (17%) than in that estimated earlier for ITP patients [1].
- CL/F decreased in older patients with cancer (>50 years), and did not depend on weight. Female and Asian patients with cancer had lower CL/F, consistent with findings in ITP patients and HVs.

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) Abstract 1502 [www.page-meeting.org/?abstract=1502].