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 pharmacokinetics (PK) of eltorombopag in healthy volunteers and patients with ITP have been described previously. 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 eltorombopag exposure.

Objectives

- To develop a semi-physiological model describing the relationship between plasma eltorombopag 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 to compute eltorombopag 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, splecnecomy, 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 PK/PD model was implemented with 3 PK and 4 PD compartments (Fig 1).
- Stimulation of PLTc production by eltorombopag was achieved through increases in order production rate of platelet precursors (KiN); KiN increased linearly with eltorombopag 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 eltorombopag 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*BASEx).
- 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 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.

Results

Healthy Volunteer Results (Table 1):
- 32% increase in KiN for each 1 mg/mL of eltorombopag.
- Blood platelet half-life of 105 hr.
- Females were less sensitive to eltorombopag (36% lower SLOP).
- PLTc were higher in East Asian race and in females because of greater exposure to eltorombopag (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 eltorombopag (P1) with a 58% increase in KiN for each 1 mg/mL of eltorombopag; non-responders (19%) had SLOP≈0.
- Blood platelet half-life of 8 hr.
- Females were more sensitive to eltorombopag (2.4-fold higher SLOP than males) as well as older patients (SLOP ranged from 0.15 to 1.14 mg/mL in male ITP patients of 18 to 85 years old).
- PLTc were higher in East Asian race > (Age >85 years) > (baseline >15 G/L) > Females > Corticosteroid use either because of greater PD response or greater exposure to eltorombopag (Fig 1).
- 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).

Conclusions

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

References