A Novel Framework of Long-term Prediction of Integrase Inhibitors for Treatment Naïve Patients

Ryuki Kubota, Toru Ishibashi, Yoshihiro Wajima
Clinical Pharmacology & Pharmacokinetics, Shionogi & Co. Ltd., Osaka, Japan

Abstract

Objective: Daltegravir (DTG, SGSK1349572) is an unboosted, once daily integrase inhibitor currently under development for the treatment of HIV infection. A mathematical representation of long-term viral responses for integrase inhibitors remains challenging because it must include phenomena that are difficult to model such as resistance, background therapy and adherence. The objective was to develop a framework that describes complicated interactions in long-term treatment with integrase inhibitors, and that predicts efficacy at 96 weeks in Phase 3 clinical trials.

Methods: A simple PK/PD model for virologic response, which was developed previously [1], was used to predict HIV-1 RNA time courses in treatment naïve patients. The model was modified for incorporating resistance, adherence, subject dropout and the effect of background therapy (dual nucleoside reverse transcriptase inhibitors). Viral load influenced the probability of resistance-associated mutations. The basic model parameters were based on the estimates from Phase 2a 10-day monotherapy studies. Some of model parameters were adjusted so that the model described the observed data for up to 24 weeks in SPRING-1 [2] and STARTMARK [3, 4]. The model was used for predicting long-term viral responses for up to 96 weeks to simulate the results for a treatment-naïve Phase 3 study.

Results: Predicted proportion (%) simulation interval) of patients with <50 copies/mL HIV-1 RNA at 24 weeks were simulated as 90.0% (83.9%-96.0%), 96.0% (90.0%-100.0%), and 96.0% (92.0%-100.0%) at 10, 25 and 50 mg QD of DTG, respectively, and 92.0% (85.9%-96.0%) at 400 mg BID of raltegravir (RAL). These predictions were reasonably consistent with the data in SPRING-1 and STARTMARK. DTG was predicted to suppress viral loads to less than 50 copies/mL, over a long duration: 82.0% (73.9%-90.0%) at 10 mg QD, 92.0% (84.0%-96.0%) in the 25 mg QD, and 92.0% (86.0%-96.1%) at 50 mg QD at 96 weeks, while 84.0% (78.9%-92.3%) at 400 mg BID of RAL.

Conclusions: We propose a novel framework for long-term prediction of efficacy with integrase inhibitors. The simulation shows durable efficacy of DTG for treatment naïve patients and supports the dose selection of 50 mg QD in Phase 3 studies.

Introduction

Integrase Inhibitors for Treatment Naïve Patients

Figure 1. A Model of Long-term prediction for Integrase Inhibitors

Methods

The simple PK/PD model for virologic response, which was developed previously based on the estimates from Phase 2a 10-day monotherapy studies[1], was extended for long-term prediction in treatment naïve patients.

Figure 1. A Model of Long-term prediction for Integrase Inhibitors

Expected viral counts

Figure 3. Long-term Prediction up to 96 Weeks

Conclusions

We propose a novel framework for long-term prediction of efficacy with integrase inhibitors.

The simulation shows durable efficacy of DTG for treatment naïve patients and supports the dose selection of 50 mg QD in Phase 3 studies.

References