Introduction

The treatment of diabetes is a primary public health concern for effective HbA1c (glycosylated haemoglobin) control. HbA1c is a biomarker that can be used to assess the degree to which the level of blood glucose has been controlled over the past 8–12 weeks. This parameter is also considered a better biomarker for diabetes treatment than the traditional endpoint FPG (fasting plasma glucose) because it is less affected by intercurrent illness (excluding acute diabetic episodes). HbA1c is determined by an enzymatic reaction that is catalyzed by glucose-6-phosphate dehydrogenase (EC 1.1.1.49), leading to the formation of the glycated protein HbA1c (1). A higher proportion of HbA1c indicates an increased risk of diabetes-related complications (2). The PK/PD model for tesaglitazar is based on the following basic principles:

1. The AICR (American Institute for Cancer Research) – the proportion of Hb that is glycosylated increases continuously with RBC age.
2. The glycosylation of Hb is a function of blood glucose concentration and duration of exposure, with a half-life of 11 days (3, 4).

Methods

We tested four different hypotheses for the tesaglitazar-induced effect on Hb. These were:

1. The model (Figure 3, Table 3) – not the model (Figure 3).
   - FPG on the X-axis, Hb on the Y-axis, and HbA1c on the Z-axis.
   - The model was based on the following basic principles:
     - The physiological process of RBC formation (kin) and destruction (kout) was described by the following equation:
     \[ K_{\text{kin}} \times \text{age} - K_{\text{kout}} \times \text{age} = 0 \]
     - The rate of RBC formation, Kin, was calculated using a function of the age and gender of the patient. The rate of RBC destruction, Kout, was calculated using the age and gender of the patient.

Results

Demographics

In total, 412 patients were included in the analysis (242 men and 170 women). Of the 412 patients, 130 were naïve to tesaglitazar (0.1 to 3.0 mg). An open-label pioglitazone 45 mg arm was also included in this study, but not included in the model. In addition, to perform an exploratory analysis to evaluate four different hypotheses for the tesaglitazar effect on Hb.

Objective

The model and its mechanism-based PK/PD model were evaluated in the following way:

- The model predicted the effect of tesaglitazar on Hb and HbA1c in patients with type 2 diabetes.
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Pharmacokinetics

The PK results have been presented earlier (5) and are only summarized here.

The PK/PD model was based on the following basic principles:

1. The PKs of tesaglitazar were well described by a one-compartment model with first-order absorption and elimination.
2. Tesaglitazar oral clearance (CL/F) was correlated with creatinine clearance (CrCL) and no significant effects of gender, age, or body weight and renal function.
3. Non-selective elimination of RBC produced the lowest objective function value, in combination with reasonable parameter estimates.
4. A gender difference in EC50 was found.

Table 1. Demographics and baseline patient characteristics

Table 2. Population PK/PD parameters for the mechanism-based FPG, Hb and HbA1c model (relative SE, %)

Table 3. Population PK/PD parameters for the mechanism-based FPG, Hb and HbA1c model (relative SE, %)

Conclusions

The model indicated that a plausible explanation for the tesaglitazar effect on Hb is caused by haemodilution of RBC, but further studies are needed to better understand this PK/PK-mediating effect.

References