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112.THALASSEMIA AND GLOBIN GENE REGULATION

Pharmacokinetics (PK) of Deferasirox in Transfusion Dependent Thalassemia

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Iron overload is a major cause of organ dysfunction and death in transfusion-dependent thalassemia (TDT) and advances in iron chelation are urgently needed. The iron chelator, deferasirox, is widely used in TDT, however, many patients accumulate iron despite taking maximum recommended doses and many experience dose-limiting toxicity, including renal and liver failure. There is high inter-individual variability in the plasma concentrations of patients taking comparable deferasirox doses and low exposure correlates with inadequate chelation response. The cause of variable drug levels remains unknown, in part because prior deferasirox PK studies primarily include limited sample sizes and/or homogenous patients. There is an urgent unmet need to determine (1) what patient characteristics contribute to the observed variability in deferasirox-plasma concentrations, and (2) how dosing strategies can be tailored to achieve optimal therapeutic plasma-drug concentrations in all patients.

We initiated a 2 year, single center observational pharmacokinetic (PK) pilot study to describe the PK of deferasirox in a diverse group of TDT patients from 2 years old through adulthood with a goal accrual of 50 patients. Our aim is to develop a population PK (popPK) model of deferasirox that will be evaluated in a future prospective study to individualize dosing and optimize exposure. The eligibility criteria are broad to capture a diverse population. Patients are eligible if they: 1) have a diagnosis of TDT, 2) are taking deferasirox, and 3) are able to provide informed consent (or have a guardian provide informed consent). For quantification of plasma deferasirox concentrations, 0.5 ml of whole blood are collected prior to transfusions at 4 regularly scheduled transfusion visits. Samples are then analyzed by a validated high performance liquid chromatography assay. Baseline labs, liver iron concentration and information on concomitant chelators are collected at the start of the study and labs, fed/fasted state, time and dose of last deferasirox, deferasirox regimen, and concomitant chelators are collected at each study visit. The planned analysis is to use nonlinear mixed effect modeling to calculate drug exposure and develop the popPK model.

We have enrolled 39 patients with TDT, including 27 patients with beta thalassemia major, 10 patients with hemoglobin E beta thalassemia, 12 patients with hemoglobin H constant spring and one patient with beta thalassemia intermedia. Median age is 28 years old, with a range from 6 - 63 years old. Pre-study iron status also varied considerably, with median liver iron concentration 4.5 mg/g (range 1.5 -30 mg/g) and median ferritin 1500 ug/L (range 460 - 5600 ug/L).

Thirty one patients have completed the study and 141 samples have been collected. Initial analysis of the first 15 patients who completed the study show a wide range of steady state plasma-deferasirox concentrations, consistent with prior reports. The means for the 4 samples collected per patient were calculated and found to have a median of 36.3 ug/ml with a range of 13.4 - 56.0 ug/ml. For the individual sample collections, the range of plasma deferasirox concentrations was even greater (0.18 - 99.9 ug/ml). These results need to be analyzed further to account for the dosing regimen, iron burden and other individual patient characteristics.

In this study, we also collected genomic DNA from the buffy coat to evaluate the impact of single nucleotide polymorphisms in enzymes involved in drug metabolism and distribution. Once all data is collected, we will evaluate whether patient age, weight, laboratory values, fed/fasted state, concomitant chelators or pharmacogenomics impact deferasirox serum concentrations and can inform individualized deferasirox dosing. This study is unique, unlike prior deferasirox PK studies which collected intensive PK, we are using sparse sampling to collect real world data on deferasirox at steady state in TDT patients. Our hope is that this study will enable safer more effective dosing of deferasirox in patients with TDT.

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