Analytical characterization of glucocerebrosidase enzymatic activity using UV and FLUO detection for the individualization of Gaucher type I patients using a population pharmacokinetic approach

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[Objetivo] The aims of the current work are (i) to assess the relationship between ultraviolet (UV) and fluorescense (FLUO) observations of glucocerebrosidase enzymatic activity, and (ii) to develop a population pharmacokinetic model of enzyme activity in Gaucher disease type I.

[Metodos] A prospective follow-up, semi-experimental multicentric study was conducted in four public hospitals from June 2010 to December 2017. Continuous glucocerebrosidase activity (GBA) observations were collected 10 and 75 minutes pre- and post-administration, respectively, during therapeutic drug monitoring (TDM) up to one year after the patient's enrolment. GBA observations in leukocyte and monocyte were available for the analysis. Two different validated analytical methods were used, which measured GBA1 (UV) and GBA1,2,3 (FLUO) in leukocytes and monocytes. GBA in leukocytes and monocytes were described with compartmental models parameterized in apparent volumes of distribution, and first-order distribution and elimination clearances. Between subject variability (IIV) on pharmacokinetic (PK) model parameters was modeled exponentially, and residual variability was described with an additive model on the logarithmic scale. The covariate analysis was carried out by the stepwise covariate modelling (SCM). The significance of potential covariates was systematically evaluated in a stepwise forward selection (ΔOFV <3.84 points, $p<0.05$) one at a time. Model evaluation was performed through prediction-corrected visual predictive checks and bootstrap analysis.

[Resultados y Discusión] A total number of 25 individuals with 266 GBA in leucocytes and monocytes observations were included in the PK analysis. The base population PK model contains a two concatenated compartments to describe GBA observations in leucocytes and monocytes, respectively. The structural model assumes a zero-order endogenous production of GBA to describe a constant synthesis of the endogenous enzyme. A first-order distribution of GBA from leucocytes into monocytes and a first-order elimination process of GBA from monocytes properly modelled GBA profiles. An exponential time-dependency effect on CL1 statistically improved the description of the data ($p<0.01$), demonstrating a roughly 10% decrease over time in CL1 after 3 months of ERT.

[Conclusiones] A population pharmacokinetic model has been developed and successfully qualified to explain the leukokycte and monocyte GBA-time profiles following intravenous administration of ERT in GD1 patients.