Simulation-Based Assessment of Insulin Lispro Dose Titration Algorithms Using a Model of Glucose-Insulin-Glucagon Dynamics

Xiaosu Ma1*, Jenny Y Chien1, Jennal Johnson1, James Malone1, Vikram Sinha2

1Eli Lilly and Company, Indianapolis, IN; 2Food and Drug Administration, Silver Spring, MD

Objective: Evaluate glycemic outcome in patients with type 2 diabetes mellitus (T2DM) treated with insulin lispro (L) following various dose titration algorithms using a glucose-insulin-glucagon (GIG) model [1].

Methods: The GIG model included L and Glargine (G), and effect of Metformin (MET) on glucodynamics. It was used to simulate various dosing algorithms for patients administering basal G and pre-prandial L. The pharmacokinetics (PK) of both insulins was described by a one-compartment model with first-order absorption. The effect of MET on inhibition of glucose production was modeled as an effect compartment. The model was prospectively used to simulate the condition and design of the AUTONOMY study [2]: patients initiating with a single breakfast injection of L, with dose adjusted based on pre-lunch glucose from the previous day (Q1D) or 3-days until reaching glucose target. Lunch and dinner doses were titrated sequentially following the same algorithm. Treatment with G and MET only and two reference comparator algorithms [3] were also evaluated. Simulated 7-points self-monitoring of blood glucose (SMBG) was used to predict hypoglycemia rate. Endpoint HbA1c was predicted using a time-course model based on average daily glucose.

Results: Approximately 250 T2DM patients were simulated for each arm. HbA1c, fasting glucose, hypoglycemia rate and percent patients achieving HbA1c target (<7.0%) were simulated and compared with study outcome. HbA1c was predicted to achieve approximately 1.1% reduction from baseline using the Q1D algorithms compared to other algorithms (Figure 1).

Conclusions: Model-based simulation is an efficient approach to evaluate the impact of dosing algorithms on glycemic control in treatment of diabetes. The model predicted the results of the clinical trial and further supported the effectiveness of the recommended L self-titration algorithms.

References: