Model-based Meta-analysis of GLP-1 Agonist Liraglutide Intervention of Obesity and Glucose Intolerance Disease Progression in Type 2 Diabetes

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Objectives: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder that is characterized by a progressive loss of insulin sensitivity and resultant chronic hyperglycemia. Obesity has been recognized as a major risk for T2DM through deterioration of insulin resistance. The ability to simultaneously target deteriorated glycemic control and obesity represents the ideal approach for treating T2DM; unfortunately conventional glucose-lowering therapies commonly result in weight gain. Liraglutide, a GLP-1 agonist that promotes insulin secretion and accelerates weight loss simultaneously, has been approved for treatment of T2DM and obesity. This study aims to develop a model to quantitatively describe liraglutide effects on glycemic control and weight management simultaneously in T2DM.

Methods: A database of study-level aggregate data of body weight, fasting plasma glucose (FPG) and HbA1c in T2DM patients after placebo or liraglutide monotherapy (daily dose ranged from 0.9 to 3.0 mg) was constructed from published clinical studies. Model-based meta-analysis of liraglutide weight reduction effects and glycemic control activity was conducted sequentially with a Stochastic Approximation Expectation Maximization algorithm in NONMEM.

Results: A mechanism-based model was developed by integrating temporal cascades of liraglutide PK, inhibition of β-cell deterioration, induction of pancreatic insulin secretion, and inhibition of weight gain-associated insulin resistance with FPG and HbA1c homeostasis. This model adequately described the time-course of body weight, FPG and HbA1c dynamics following placebo and liraglutide monotherapy, where liraglutide decreased weight and reduced FPG and HbA1c concentrations in a dose-dependent manner. The model-predicted HbA1c dynamics reasonably replicated external data, illustrating the robustness of this model. Furthermore, the good agreement between model-predicted insulin resistance index and literature reported HOMA-IR assessments supported the applicability of this model (Fig.1).

Conclusions: A quantitative model was developed and successfully characterized the time-course of glycemic and obesity biomarkers following liraglutide monotherapy in T2DM patients. This model is based on codifying multiple regulatory mechanisms of liraglutide action and should provide a platform for probing optimized liraglutide-based combination therapy in T2DM.

Figure 1: Model-predicted mean profiles of changes in weight, fasting serum glucose (FPG), homeostasis model assessment of insulin resistance (HOMA-IR) and HbA1c after placebo or liraglutide monotherapy in patients with T2DM