Leveraging a Diabetes QSP Model to Drive Decisions in Target ID and Validation for a Proinsulin Program

Abstract

Objectives: Proinsulin is a precursor to insulin that is co-secreted into the blood by the beta cell as a result of incomplete processing. Circulating proinsulin levels increase with increasing insulin resistance in type 2 diabetes mellitus (T2DM). Unlike insulin, proinsulin has limited activity on the insulin receptor. To assess whether the development of peptides engineered to convert proinsulin to insulin in the blood would provide therapeutic value in T2DM, we leveraged a diabetes quantitative systems pharmacology (QSP) model (a physiologically based computational model of glucose homeostasis in humans), internal clinical datasets, and external data from the literature.

Methods: In silico hypothesis testing included 1) the addition and qualification of proinsulin biology into our diabetes QSP model; 2) the creation of virtual patients (VP) to determine whether proinsulin conversion during model building may provide value to a subset of patients with T2DM based on phenotypic traits, either as a monotherapy or in addition to standards of care (metformin and sulfonylurea); and 3) the simulation of a phase 3 clinical trial with relevant endpoints (including HbA1c and glucose, insulin, and proinsulin) and additional mechanistic readouts (changes in circulating hormones and metabolites during meals and glucose tolerance tests) to interrogate and interpret results.

Results: As monotherapy, proinsulin conversion to insulin led to a ~0.2% reduction in HbA1c in diabetic VP with less severe effects (~0.1%) when added to a standard of care. Virtual patients with higher proinsulin:insulin ratios at baseline showed the greatest reductions. However, to achieve a clinically meaningful HbA1c reduction of 20.5%, most VPs needed ratios above the reported physiological range. The minimal influence of proinsulin conversion could be explained by the proinsulin secretion and degradation rates relative to respective rates for insulin; these system dynamics were a key learning from the QSP model.

Conclusions: The lack of projected impact on HbA1c through conversion of proinsulin to insulin was not intuitive prior to the in silico hypothesis testing using QSP approaches. The simulation results were examined and challenged with rigor both quantitatively and qualitatively and led to a recommendation not to pursue proinsulin conversion as a potential T2DM therapy. The QSP modeling approach was chosen to capture not only the dynamic interplay between proinsulin and insulin kinetics but their impact on a complex multi-organ system that maintains glucose homeostasis in the body. By thoroughly evaluating the putative therapeutic in diabetic VPs in a simulated Phase 3 setting, we were able to generate sufficient scientific rationale for the termination decision. This effort demonstrates how in silico hypothesis testing through QSP modeling may aid in target identification and validation efforts in the discovery space, conserving R&D resources for targets with greater probability of clinical success.

BACKGROUND

An existing quantitative systems pharmacology (QSP) model based on human and preclinical data has been leveraged to inform discovery and early development questions in diabetes.

PROINSULIN VS INSULIN: CONCENTRATION-EFFECT RELATIONSHIP

Empirical evaluations of the data in the literature suggested that conversion of proinsulin (within the range typically found in the blood) to insulin would result in physiologically meaningful changes in insulin.

IN SILICO HYPOTHESIS TESTING USING THE DIABETES QSP

Key questions:

- Will the conversion of circulating proinsulin to insulin reduce hyperglycemia in T2DM?
- What impact will background therapies of metformin or sulfonylurea have on the efficacy of a proinsulin-converting drug in T2DM?
- How variable do proinsulin:insulin ratios need to be to capture not only the dynamic interplay between proinsulin and insulin kinetics but their impact on a complex multi-organ system that maintains glucose homeostasis in the body?

Step 1: Incorporation of proinsulin biology and a putative proinsulin proinsulin conversion into the diabetes QSP model. Qualitative and quantitative testing of the proinsulin build as well as the base model were performed.

Step 2: Virtual patients (VP) designed to represent various segments of the spectrum of healthy through T2DM subjects. Attributes of VPs were cross-checked with literature and internal data.

Step 3: In silico hypothesis testing was performed using the QSP model and alternative VPs to examine efficacy with proinsulin to insulin conversion therapy. Therapeutic conversion of proinsulin to insulin showed a diminutive effect on circulating insulin, resulting in reductions in HbA1c that were not clinically meaningful, even in combination with metformin (an insulin sensitizer) or sulfonylureas (insulin secretagogues).

Virtual patients with higher proinsulin:insulin ratios showed increased reductions in HbA1c with proinsulin conversion therapy. However, ratios higher than physiologically relevant were needed to achieve desirable effects.

Though circulating levels of proinsulin and insulin are often comparable in T2DM, secretion and degradation rates of proinsulin are much lower than insulin rates, preventing the conversion of proinsulin from having much impact on insulin levels/glucose/HbA1c.

Increasing the secretion and degradation rates (and, therefore, the total flux of proinsulin) until they approach those rates for insulin improved the therapeutic potential but are not realistic, as clearance rates needed to maintain observed proinsulin levels approached that of insulin, which is not as observed.

SUMMARY AND CONCLUSIONS

- The conversion of circulating proinsulin to insulin resulted in small reductions in HbA1c that were not viable for development of a proinsulin to insulin based conversion therapy for T2DM, even in combination with metformin or sulfonylurea.
- The larger the baseline proinsulin:insulin ratio, the greater the improvement in glycemia with treatment. However, ratios needed for this level of change were not physiologically relevant (ratios >2).
- Data in the literature on proinsulin secretion rates are limited and variable. However, simulations exploring proinsulin kinetics demonstrated that unreasonably high secretion rates are required for clinically meaningful efficacy. This low level of efficacy combined with the unlikelihood of kinetic conditions needed to achieve it resulted in a no-go for the proinsulin program.
- This no-go was based primarily on the results of the in silico testing using QSP described, saving time and money better spent on projects with greater probability of success.

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