Insilico Study Examining Initiation of Insulin Glargine U100 in Virtual Subjects with T2DM

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Background

Early and appropriate insulin therapy can be an essential part of an individualized treatment strategy in uncontrolled T2DM[1]. A primary barrier for insulin use is the potential for hypoglycemia, despite lowering blood glucose (BG) levels to target ranges. Also, as 95% of T2DM subjects are managed in general clinical practice settings, it is unclear to clinicians when and how insulin should be initiated and they are challenged when managing diabetes care that includes insulin therapy[2].

The availability of once daily, long-acting insulin glargine 100 u/ml (Gla-100; Lantus®) has provided a means to offset clinical inertia associated with insulin treatment for T2DM[3]. Safely initiating the insulin with consequent dosage adjustment based on fasting blood glucose (FBG) through a web-based, easy-to-use insulin dosing titration algorithm is a valuable tool for clinicians, and a strategy to help patients achieve a target glucose range with fewer hypo-glycemia episodes[4].

This insilico study examines the glucose control of virtual adults with T2DM using such a webtool to recommend initial and ongoing Lantus U-100 insulin doses while imposing lifestyle events such as exercise, illness and overeating, to optimally manage BG to a specified target range using three titration rules (TRs).

Methods

Protocol:

One hundred virtual T2DM subjects in the Diabetes Mellitus Metabolic Simulator (DMMS, TEGvirginia.com) received initial dosing of insulin Lantus at 0.2 U/kg to reach a steady state of insulin-on-board over one week. Subjects then submitted their FBG to the webtool daily, reported any hypoglycemia experience, and received dose titration recommendations to achieve a designated target BG range (Table 1) for 4 months.

Table 1. Titration Rules

Titration Rules	Target Range for Fasting Blood Glucose	Insulin Dose Recommendations
TR1	Fasting BG Target Range: 90 – 130 mg/dL	Standard increase units every 3 days if FBG > 130 mg/dL
TR2	Fasting BG Target Range: 90 – 130 mg/dL	Aggressive increase every 3 days if FBG > 180 mg/dL followed by Standard increase every 3 days if FBG > 130 mg/dL
TR3	Fasting BG Target Range: 110 – 150 mg/dL	Standard increase every 3 days if FBG > 150 mg/dL

The population was studied separately under all 3 TRs. After attempts to reach a stable dose in target (no adjustments for 10 days and 5 consecutive days with FBG in target range), lifestyle interventions were introduced to perturb the subjects' BG and examine the TR ability to maintain control safely. The subjects were 100% compliant in following the dosing recommendations and completely honest in their reporting.

Models

Insulin glargine U100 Lantus®

Proprietary pharmacokinetic and pharmacodynamic data were provided by Sanofi Aventis GmbH for design of this long-acting insulin model

Exercise:

Two consecutive days of high intensity exercise (HI) were imposed to lower FBG on the following mornings. The biphasic exercise model was designed using study data[5] examining the short- and longer-term effects of HI on BG levels in people with T2DM. The short-term effect (during and within 3 hours of HI exercise) was primarily characterized by an increase in glucose utilization (GU), and the longer-term effect characterized by a reduction in endogenous glucose production (EGP) causing lower FBG the following mornings.

Illness:

Illness was present 2 consecutive days with recovery over the following third day to cause hyperglycemia. The illness model used here increases EGP and was achieved entirely through modification of the k_{p1} parameter[6] targeting a mean increase of 70 mg/dL during the periods of illness[7].

Overeating:

The subjects were given 3 very large meals (75 gm carbohydrates) for 2 consecutive days to simulate holiday feasting to cause hyper-glycemia. This is in contrast to the daily regular meals (40 gm, 60 gm, 60 gm CHO for breakfast, lunch and dinner respectively).

Endpoints

Efficacy measures included mean time-to-target assigned BG range, change in mean FBG, BG, HBA1c and HBGI from baseline to 4 months, number of hypoglycemia events as well as percent time below, in and above target range. Metrics specific to the intervention effects include number of webtool adjustments and HBGI, LBGI risk. Population statistics include M ± SD calculated on per-subject means.

References:
1. Open Obesity Journal, 2014; 6:70-75,
2. Diabetes Medicine 2012;29:682-9.
3. Annals of Pharmacotherapy 2002;36:1019-1027.
4. J Diabetes Science and Technology 2016;19(5):1122-1129.
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Results

Three subjects experienced hypoglycemia BG<70 mg/dL at the initiation of weight-based insulin and the dose was reduced. Most subjects reached target (TR1=98; TR2=98; TR3=96) safely (Table 2) within 2-3 weeks of webtool dosing recommendations. All subjects reached their target FBG range.

Table 2. Glucose Control Metrics with no Interventions, During Webtool Management

BG Control Metrics	TR 1 Target Range 90-130 mg/dL	TR 2 Target Range 90-130 mg/dL	TR 3 Target Range 110-150 mg/dL
Mean Baseline FBG (mg/dL)	155 ± 40	155 ± 40	155 ± 40
Mean In-Target FBG (mg/dL)	118 ± 11	118 ± 11	118 ± 11
Mean Baseline BG (mg/dL)	186 ± 37	186 ± 37	186 ± 37
Mean In-Target BG (mg/dL)	158 ± 25	158 ± 25	168 ± 26
Mean HbA1c Reduction (eA1c)	0.9%	1.0%	0.6%
Mean time-to-Target (Days)	20 ± 19	19 ± 18	14 ± 12
% Time Below Target	0.06 ± 0.31	0.06± 0.31	2.89±11.68
%Time In Target	34.15 ±18.17	34.16±18.16	41.06 ± 17.33
% Time Above Target	65.79 ± 18.23	65.78±18.21	56.05±20.15

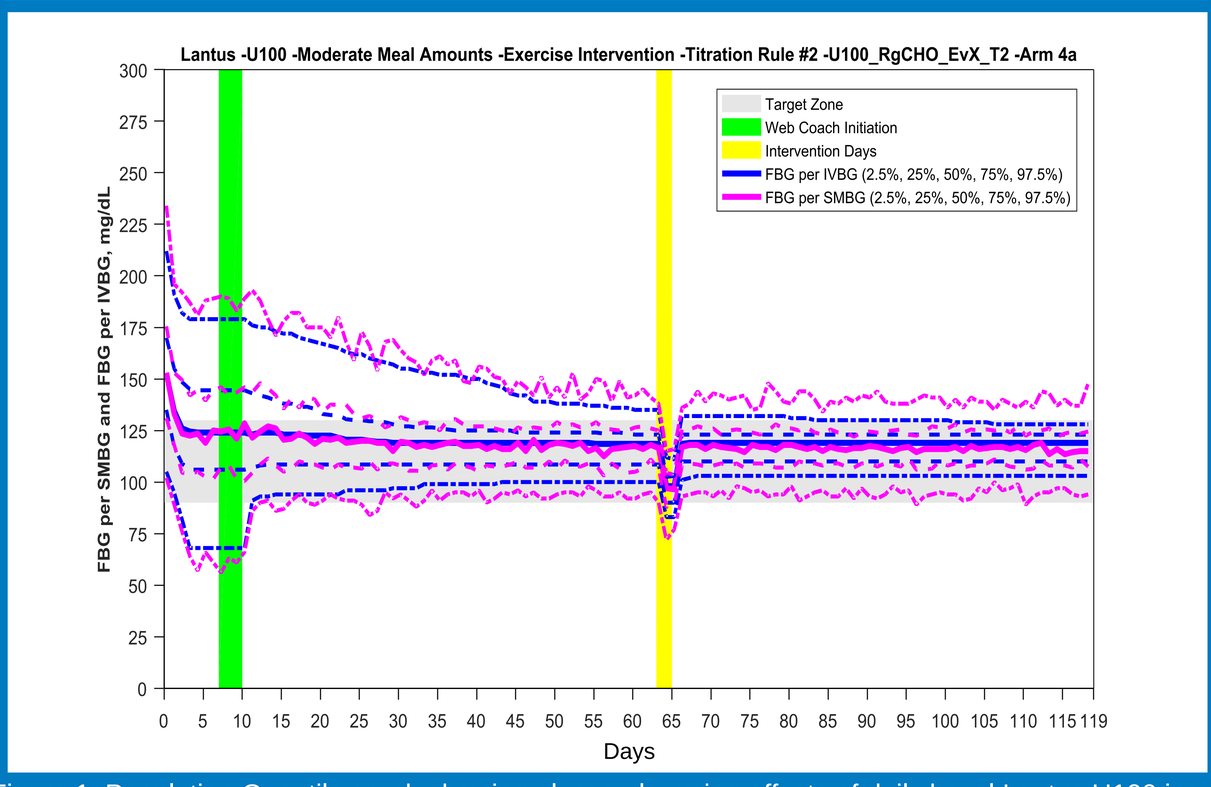

Figure 1. Population Quantile graph showing glucose-lowering effects of daily basal Lantus U100 insulin dosing titration per TR 2. While exercise caused lower FBG, the recommended insulin dose maintained BG safely in target range.

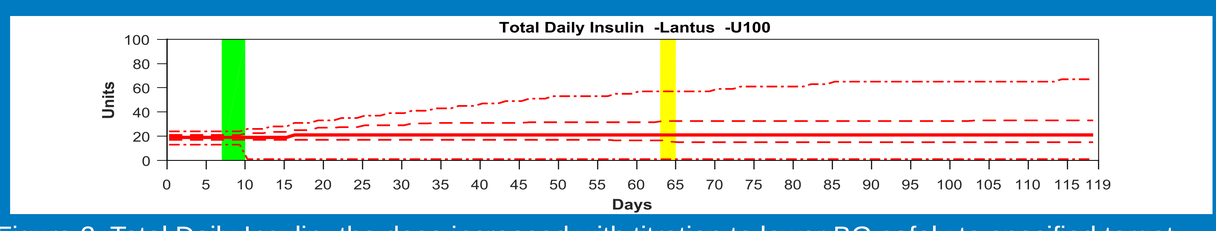

Figure 2. Total Daily Insulin- the dose increased with titration to lower BG safely to specified target range over the duration of the simulation study period.

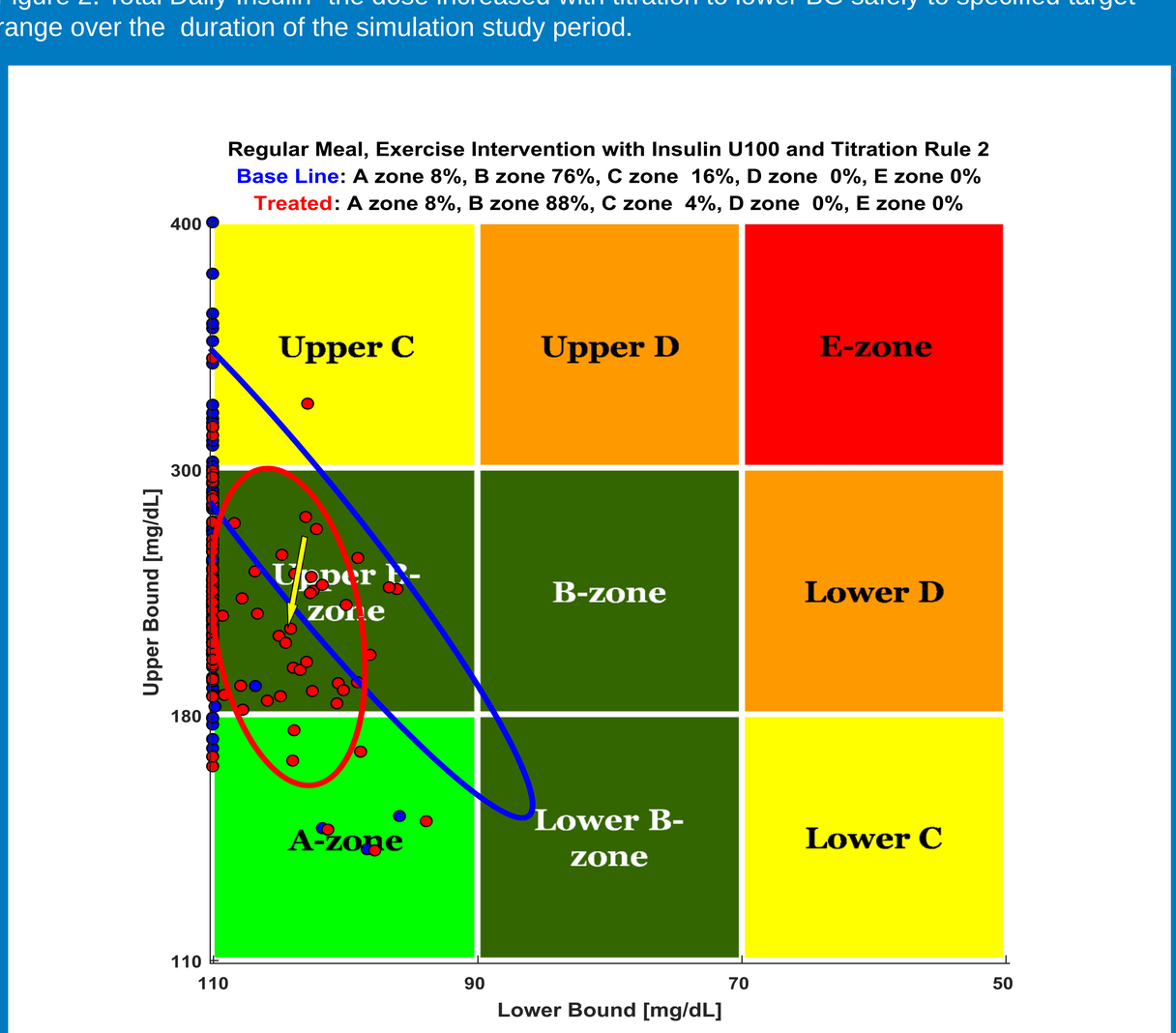

Figure 3. CVGA graph demonstrates the shift of extremes in BG to zones of better control, and better outcomes while avoiding dangerous hypoglycemia in subjects with T2DM. The "treated" data points include FBGs from the entire titration period.

Conclusions

The insulin glargine U100 titration recommendations delivered by the webtool were effective in safely initiating and optimizing glargine U100 in 100 insulin-naïve T2DM subjects to the specified target ranges with low risk of hypoglycemia, even when exercise, illness and overeating occurred to disrupt BG control,.

These findings are similar to the clinical study[4], and suggest the webtool would provide valuable support to General practitioners initiating insulin in their patients with T2DM.

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