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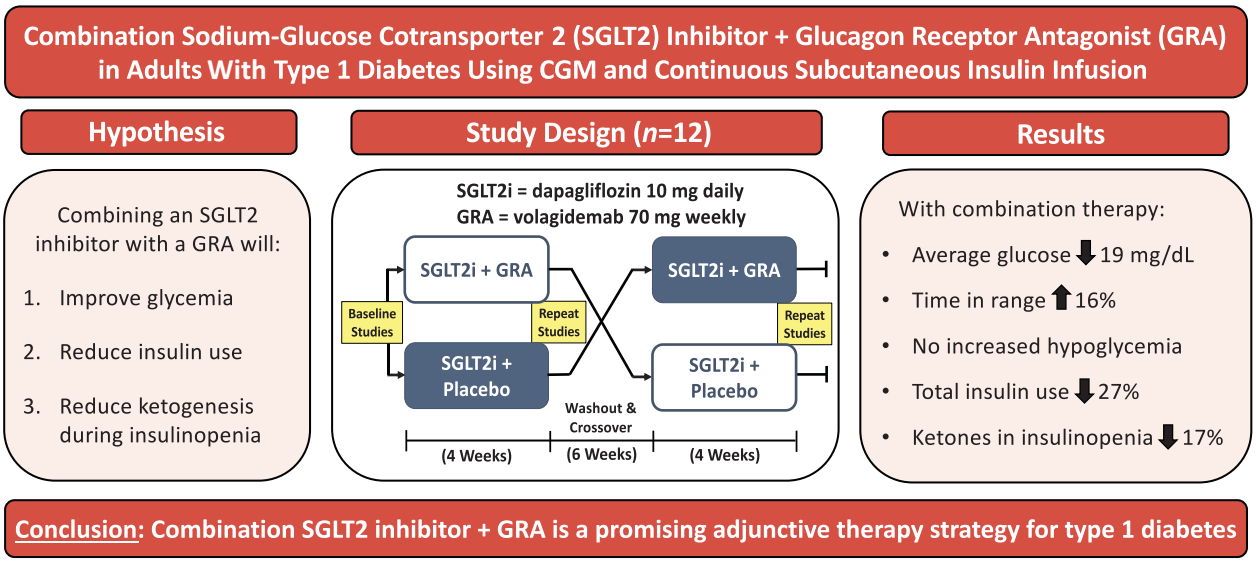

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To investigate the efficacy of insulin-adjunctive combination therapy using a sodium–glucose cotransporter 2 (SGLT2) inhibitor and a glucagon receptor antagonist (GRA) in type 1 diabetes.
- **What is the specific question(s) we wanted to answer?**
  In this study, we aimed to determine whether combination SGLT2 inhibitor and GRA therapy could improve glycemic control, reduce insulin requirements, and mitigate ketogenesis during insulinopenia.
- **What did we find?**
  Combination therapy significantly improved glycemic control and reduced insulin use. Also, the addition of a GRA to SGLT2 inhibitor therapy slowed ketogenesis during insulinopenia.
- **What are the implications of our findings?**
  Blocking glucagon enhances the therapeutic effects of SGLT2 inhibition, offering a promising strategy to improve glycemic control and reduce insulin dosing while mitigating the risk of diabetic ketoacidosis in type 1 diabetes.

Combination SGLT2 Inhibitor and Glucagon Receptor Antagonist Therapy in Type 1 Diabetes: A Randomized Clinical Trial

Schafer C. Boeder,[1] Robert L. Thomas,[1] Melissa J. Le Roux,[1] Erin R. Giovannetti,[1] Justin M. Gregory,[2] and Jeremy H. Pettus[1]

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ORIGINAL ARTICLE

OBJECTIVE

To examine the effects of insulin-adjunctive therapy with a sodium–glucose cotransporter 2 (SGLT2) inhibitor and a glucagon receptor antagonist (GRA) on glycemia, insulin use, and ketogenesis during insulinopenia in type 1 diabetes.

RESEARCH DESIGN AND METHODS

In a randomized, double-blind, placebo-controlled, crossover trial we assessed the effects of adjunctive SGLT2 inhibitor therapy (dapagliflozin 10 mg daily) alone and in combination with the GRA volagidemab (70 mg weekly) in 12 adults with type 1 diabetes. Continuous glucose monitoring, insulin dosing, and insulin withdrawal tests (IWT) for measurement of glucose and ketogenesis during insulinopenia were completed during insulin-only (Baseline), SGLT2 inhibitor, and combination (SGLT2 inhibitor + GRA) therapy periods.

RESULTS

Average glucose and percent time with glucose in range (70–180 mg/dL) improved with combination therapy versus Baseline and SGLT2 inhibitor (131 vs. 150 and 138 mg/dL [$P < 0.001$ and $P = 0.01$] and 86% vs. 70% and 78% [$P < 0.001$ and $P = 0.03$], respectively) without increased hypoglycemia. Total daily insulin use decreased with combination therapy versus Baseline and SGLT2 inhibitor (0.41 vs. 0.56 and 0.52 units/kg/day [$P < 0.001$ and $P = 0.002$]). Peak β-hydroxybutyrate levels during IWT were lower with combination therapy than with SGLT2 inhibitor (2.0 vs. 2.4 mmol/L; $P = 0.048$) and similar to levels reached during the Baseline testing period (2.1 mmol/L). Participants reported enhanced treatment acceptability and satisfaction with combination therapy.

CONCLUSIONS

Glucagon antagonism enhances the therapeutic effects of SGLT2 inhibition in type 1 diabetes. Combination therapy improves glycemic control, reduces insulin dosing, and suggests a strategy to unlock the benefits of SGLT2 inhibitors while mitigating the risk of diabetic ketoacidosis.

Despite advances in insulin therapies and diabetes technologies such as continuous glucose monitoring (CGM) and automated insulin delivery systems, achieving glycemic control remains a formidable challenge for individuals living with type 1 diabetes (1). Furthermore, a substantial proportion of this population still confronts

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acute diabetes complications including diabetic ketoacidosis (DKA) and severe hypoglycemia (2). These persisting challenges underscore the pressing need for additional therapeutic strategies beyond insulin.

The sodium–glucose cotransporter 2 (SGLT2) inhibitor medications have revolutionized the treatment of type 2 diabetes, heart failure, and chronic kidney disease. However, their use in type 1 diabetes has been limited due to an increased risk of DKA. This risk, underscored by a three- to fourfold increased risk of DKA in large phase 3 studies (3,4), remains a major barrier to U.S. Food and Drug Administration approval of SGLT2 inhibitors for this group (5–7). Given the marked risk of heart failure and chronic kidney disease in individuals with type 1 diabetes, and their general difficulty in meeting glycemic goals, the potential benefits of SGLT2 inhibitors are clear. Addressing the DKA risk is therefore crucial for safely extending these benefits to patients with type 1 diabetes.

At the root of the problem is glucagon. Our research indicates that SGLT2 inhibitor therapy in patients with type 1 diabetes leads to a 37% increase in fasting glucagon levels (8). This increased glucagon presents a dual problem: it not only increases endogenous glucose production (9), thereby diminishing the glucose-lowering effect of SGLT2 inhibitors (10,11), but it also enhances ketone production, especially under insulinopenic conditions (12,13). Thus, we hypothesize that combining SGLT2 inhibition with blockade of glucagon action can both improve glycemic control by reducing endogenous glucose production and reduce the risk of DKA by suppressing ketogenesis.

The development of glucagon receptor antagonists (GRA) provides an opportunity to test our hypothesis. The GRA volagidemab, a fully human monoclonal antibody that inhibits glucagon receptor (GCGR) interaction with glucagon, has already shown promising results. We previously demonstrated that volagidemab, as an adjunct to insulin therapy in type 1 diabetes, improves glycemic control (HbA_{1c}, −0.5%) and reduces insulin use by ∼12% (14). However, the impact of GRA therapy on ketogenesis, particularly in combination with an SGLT2 inhibitor, remains unexplored. Thus, there is a strong rationale to test adjunctive SGLT2 inhibitor and GRA therapy in combination, with the goal of maximally improving glucose control and reducing insulin requirements, while mitigating the risk of DKA. Therefore, we completed a randomized, double-blind, placebo-controlled, crossover trial to evaluate the effects of insulin-adjunctive SGLT2 inhibitor therapy alone and in combination with GRA therapy in adults with type 1 diabetes. End points included glycemic control, insulin use, ketogenesis during insulinopenia, and patient-reported outcomes.

RESEARCH DESIGN AND METHODS

Study Protocol

We enrolled 12 men and women with type 1 diabetes of at least 5 years' duration. Eligibility criteria included age 18–65 years, BMI ≥18.5 kg/m^2 and weight ≥50 kg, total daily insulin dose <1 unit/kg/day, use of continuous subcutaneous insulin infusion and CGM for ≥8 weeks, and HbA_{1c} ≤9.0% (75 mmol/mol). We excluded individuals with a history of DKA or severe hypoglycemic events within the preceding 3 months and those actively using any noninsulin antihyperglycemic medication. The study protocol was approved by the institutional review board of the University of California, San Diego, and all participants provided informed consent before inclusion in the trial. Participants were instructed to maintain their regular diet and avoid major dietary changes during the clinical trial.

During the insulin-only run-in period (Baseline), we collected insulin dosing and unblinded CGM data to assess baseline insulin use and glycemic control. Participants continued using personal CGM throughout the study. They also completed a series of questionnaires for assessment of patient-reported diabetes treatment acceptability and satisfaction (Diabetes Medication Satisfaction Tool [DMSAT]), diabetes distress (Type 1-Diabetes Distress Scale [T1-DDS]), and mental well-being (World Health Organization-Five Well-Being Index [WHO-5]). Finally, participants completed an insulin withdrawal test (IWT), as described below, for measurement of changes in ketone and blood glucose levels during insulinopenia.

On the day of the IWT, participants arrived at the clinical research unit after an overnight fast of at least 8 h, avoiding bolus insulin for 2 h prior. Before starting the study, we confirmed blood glucose levels were between 80 and 180 mg/dL (4.4 and 10 mmol/L), aligning with starting criteria. A peripheral intravenous cannula was inserted into an antecubital vein for blood sampling. To induce insulinopenia and ketogenesis, we suspended insulin infusion by removing the participants' insulin pumps.

During the IWT, we measured blood glucose and β-hydroxybutyrate (BHB) levels in real time at 30- to 60-min intervals using a glucose reference analyzer (YSI 2300 Stat Plus; YSI, Yellow Springs, OH) and bedside ketone meter (Precision Xtra ketone meter; Abbott Laboratories, Abbott Park, IL). Samples for serum insulin were drawn every 30–60 min and sent for analysis. Participants consumed 200 mL water hourly. The IWT concluded at 480 min or sooner if participants met the early termination criteria (bedside ketone ≥3.0 mmol/L, bedside glucose >399 mg/dL [22.1 mmol/L], or persistent bothersome symptoms). After the test, participants received intravenous and oral fluids, a subcutaneous insulin bolus, and a meal. Basal insulin via insulin pump was resumed. Participants were discharged when symptoms had resolved, BHB was <1.0 mmol/L, and glucose was trending downward.

Following the Baseline studies, participants were randomized 1:1 in a double-blind fashion to group A or group B. Group A received the SGLT2 inhibitor dapagliflozin (10 mg daily) and the GRA volagidemab (70 mg weekly) for 4 weeks, followed by a 6-week washout period with crossover to receive SGLT2 inhibitor + placebo for 4 weeks. The sequence for group B was the reverse. We reduced total daily insulin doses at the start of each treatment period by 10% or 20% (for participants with HbA_{1c} >8.0% and ≤8.0% [64 mmol/mol], respectively) to reduce the risk of hypoglycemia. We then adjusted insulin doses weekly to target preprandial glucose levels of 80–130 mg/dL and 2-h postprandial glucose levels of <180 mg/dL. All participants received ketone meters (Precision Xtra) and were instructed to test ketones if they experienced symptoms and report to the site if the value was >1.0 mmol/L. At the end of each 4-week treatment period, the baseline studies, including collection of ambulatory insulin dosing and CGM data; questionnaires for assessment of treatment satisfaction, diabetes burden, and general well-being; and an IWT, were repeated.

CGM and Insulin Dosing Data

During the Baseline, SGLT2 inhibitor + placebo, and SGLT2 inhibitor + GRA testing periods, we collected data for 14 days of insulin dosing and 7 days of unblinded CGM (Dexcom G6; Dexcom, San Diego, CA). We assessed various CGM metrics, including average glucose, glucose SD, and glucose percent time in target range (70–180 mg/dL), percent time above range (>180 mg/dL), and percent time below range (< 70 mg/dL). Insulin dosing data—including average total daily dose, average daily basal dose, and average daily bolus dose—were collected from each participant's insulin pump.

Questionnaires

We administered validated questionnaires during the baseline and treatment periods to assess diabetes treatment acceptability and satisfaction, diabetes distress, and mental well-being. The DMSAT is a 16-item scale for a comprehensive assessment of patient acceptability and satisfaction with the use of their diabetes medication treatment regimen (15). The T1-DDS is a validated 28-item self-report scale that uses a Likert scale to score each item from 1 (not a problem) to 6 (a very serious problem) relating to how people living with diabetes felt during the prior month, providing an overall score of diabetes emotional distress (16). The WHO-5 is a short, five-item self-reported measure of current mental well-being. The WHO-5 has been found to have validity in screening for depression and in measuring outcomes in clinical trials (17).

Biochemical Analysis

Blood samples for insulin were collected in tubes with no additive and allowed to clot for 30 min. After centrifugation, serum was collected and frozen at −80°C for subsequent analysis at Quest Diagnostics by immunoassay.

Statistical Analysis

We used descriptive statistics to summarize baseline participant characteristics. Intention-to-treat methodology was followed for analysis including all randomized, treated participants. Repeated-measures one-way ANOVA with Tukey multiple comparisons test (for parametric data), Friedman test with Dunn multiple comparisons test (for nonparametric data), and a mixed-effects model (if there were missing values) were used in GraphPad Prism, version 9.5.1 (San Diego, CA), to compare outcomes from the Baseline, SGLT2 inhibitor + placebo, and SGLT2 inhibitor + GRA testing periods. Data were summarized as means and 95% CI unless otherwise indicated. Safety data were summarized descriptively.

Data and Resource Availability

The data sets generated or analyzed during the current study are available from the corresponding author on reasonable request. No novel resources were generated or analyzed during the current study.

RESULTS

Participant Characteristics

A total of 12 participants were randomly assigned, and all participants completed the study. Key baseline characteristics included median HbA_{1c} 6.7% (50 mmol/mol), BMI 25.7 kg/m^2, and duration of type 1 diabetes 24 years. (Refer to Table 1 for a detailed summary.) All participants entered the study on a hybrid closed-loop (HCL) automated insulin delivery system and continued using an HCL system for the duration of the trial.

Adjunctive Therapy Improves Glycemic Control

CGM data revealed notable improvements in glycemic control. From 150 mg/dL for Baseline, average glucose significantly improved with SGLT2 inhibitor therapy alone (138 mg/dL; $P = 0.001$) and further improved to 131 mg/dL with combination SGLT2 inhibitor + GRA ($P < 0.001$ vs. Baseline and $P = 0.01$ vs. SGLT2 inhibitor) (Fig. 1*A*). Glucose SD, representing glycemic variability, decreased for both SGLT2 inhibitor (41 mg/dL; $P = 0.02$) and combination SGLT2 inhibitor + GRA (36 mg/dL; $P < 0.001$) compared with Baseline (52 mg/dL) (Fig. 1*B*). Percent time in target glucose range (70–180 mg/dL) increased significantly, from 70% for Baseline to 78% for SGLT2 inhibitor ($P = 0.002$) and 86% for combination therapy ($P < 0.001$ vs. Baseline and $P = 0.03$ vs. SGLT2 inhibitor) (Fig. 1*C*). Percent time above target range (glucose >180 mg/dL) decreased, from 27% for Baseline to 20% for SGLT2 inhibitor ($P = 0.003$) and 12% for combination SGLT2 inhibitor + GRA ($P = 0.001$ vs. Baseline and $P = 0.03$ vs. SGLT2 inhibitor) (Fig. 1*D*). There was no difference in percent time below target range (glucose <70 mg/dL) between the testing periods (Fig. 1*E*) or in percent time with blood glucose <54 mg/dL (0.7% for Baseline, 0.4% for SGLT2 inhibitor, and 0.4% for combination SGLT2 inhibitor + GRA).

Table 1—Baseline participant characteristics ($n = 12$)

Age (years)	38 (30–55)
Female sex, % (*n*)	58 (7)
Male sex, % (*n*)	42 (5)
Weight (kg)	77.4 (65.0–84.9)
BMI (kg/m^2)	25.7 (23.3–28.7)
Type 1 diabetes duration (years)	24 (18–31)
HbA_{1c} (%)	6.7 (5.7–7.2)
HbA_{1c} (mmol/mol)	50 (39–55)

Continuous data are presented as median (interquartile range).

Combination Adjunctive Therapy Reduces Insulin Use and Improves Treatment Acceptability and Satisfaction

Average total daily insulin dose was significantly lower for combination therapy (0.41 units/kg/day) compared with that of Baseline (0.56 units/kg/day; $P < 0.001$) and SGLT2 inhibitor (0.52 units/kg/day; $P = 0.002$) testing periods (Fig. 2*A*). Similarly, average daily basal and bolus insulin doses both decreased significantly with combination therapy (Fig. 2*A*–*C*).

Patient satisfaction with their diabetes medication treatment regimen, assessed with the DMSAT, was higher for combination SGLT2 inhibitor + GRA than for Baseline ($P = 0.03$) or SGLT2 inhibitor alone ($P = 0.049$) (Fig. 2*D*). There was no difference in scores on the T1-DDS (assessment of diabetes emotional distress) or the WHO-5 (self-reported measure of current mental well-being) between the testing periods.

GRA Therapy Reduces Ketogenesis During Insulinopenia

Mean basal arterialized serum insulin concentrations prior to the start of the IWT were 11 μU/mL for Baseline, 12 μU/mL for SGLT2 inhibitor, and 8 μU/mL for combination SGLT2 inhibitor + GRA ($P = 0.04$ vs. SGLT2 inhibitor). Mean arterialized serum insulin and plasma glucose concentrations during the IWT for each testing period are

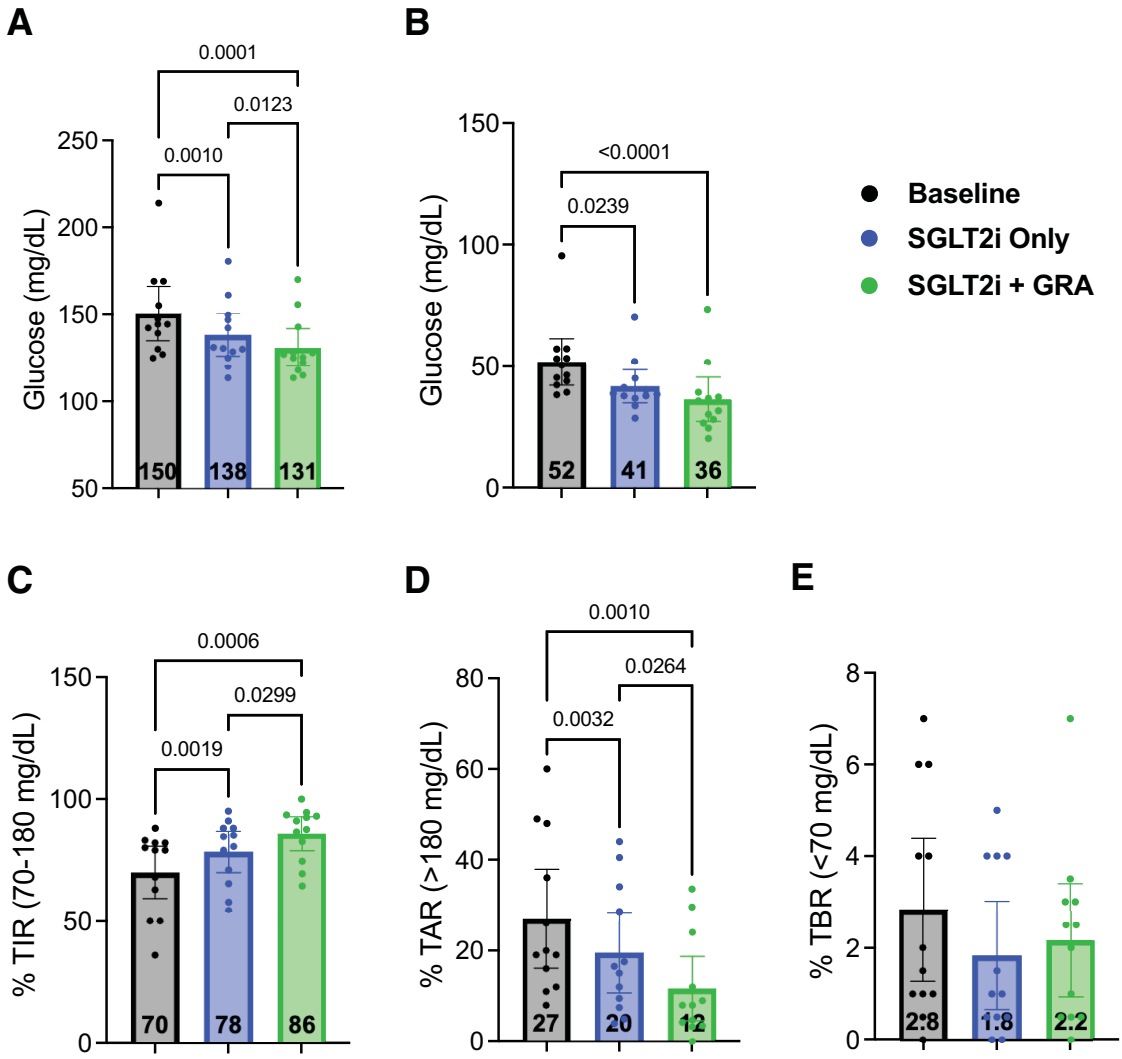

Figure 1—CGM average glucose (*A*), glucose SD (*B*), and percent time with glucose in target range (70–180 mg/dL) (*C*), above range (>180 mg/dL) (*D*), and below range (<70 mg/dL) (*E*) are shown for Baseline, SGLT2 inhibitor + placebo, and SGLT2 inhibitor + GRA testing periods. Data are summarized as means and 95% CIs. Mean values, represented with columns, are also annotated at the bottom of each column. Dots depict individual values for each participant. Significant *P* values, determined with multiple comparisons tests, are indicated above brackets. TAR, time above range; TBR, time below range; TIR, time in range.

shown in Fig. 3*A* and *C*, respectively. The peak plasma glucose concentration during IWT was significantly reduced with both therapies in comparison with Baseline (178 mg/dL for SGLT2 inhibitor and 169 mg/dL for combination therapy vs. 290 mg/dL for Baseline; $P < 0.001$ for both comparisons) (Fig. 3*D*). The increase in plasma glucose from the start of the IWT was 170 mg/dL for Baseline, 53 mg/dL for SGLT2 inhibitor therapy ($P < 0.001$ vs. Baseline), and 40 mg/dL for combination SGLT2 inhibitor + GRA therapy ($P < 0.001$ vs. Baseline).

Mean BHB concentrations during the IWT for each testing period and the number of participants who remained in the IWT at each time point are shown in Fig. 3*E*. Mean basal BHB concentrations prior to the start of the IWT were 0.2 mmol/L for Baseline, 0.5 mmol/L for SGLT2 inhibitor ($P = 0.04$ vs. Baseline), and 0.4 mmol/L for combination SGLT2 inhibitor + GRA. Some participants met early termination criteria and exited the IWT early, leading to widening CIs at later time points. Peak BHB concentrations reached during IWT were lower with combination SGLT2 inhibitor + GRA (2.0 mmol/L) than with SGLT2 inhibitor (2.4 mmol/L; $P = 0.048$) and were similar to levels reached during Baseline testing (2.1 mmol/L) (Fig. 3*F*).

The IWT was terminated at 480 min or sooner if early termination criteria were met (BHB ≥3.0 mmol/L, blood glucose >399 mg/dL [22.1 mmol/L], or persistent bothersome symptoms). The time to termination (duration) of the IWT tended to be shorter with SGLT2 inhibitor (mean 365 min) and longer with combination SGLT2 inhibitor + GRA (mean 443 min) in comparisons with Baseline (mean 398 min), though differences between testing periods were not significant (Fig. 3*B*). Most participants completed the full 480-min IWT during the combination SGLT2 inhibitor + GRA period, whereas the IWT was terminated early—due to BHB ≥3.0 mmol/L or persistent bothersome symptoms (usually nausea)—for most participants during Baseline and SGLT2 inhibitor testing periods (Fig. 3*G* and *H*). To characterize the rate of ketone formation during insulin withdrawal, we calculated a ketogenesis index (IKet) by dividing the

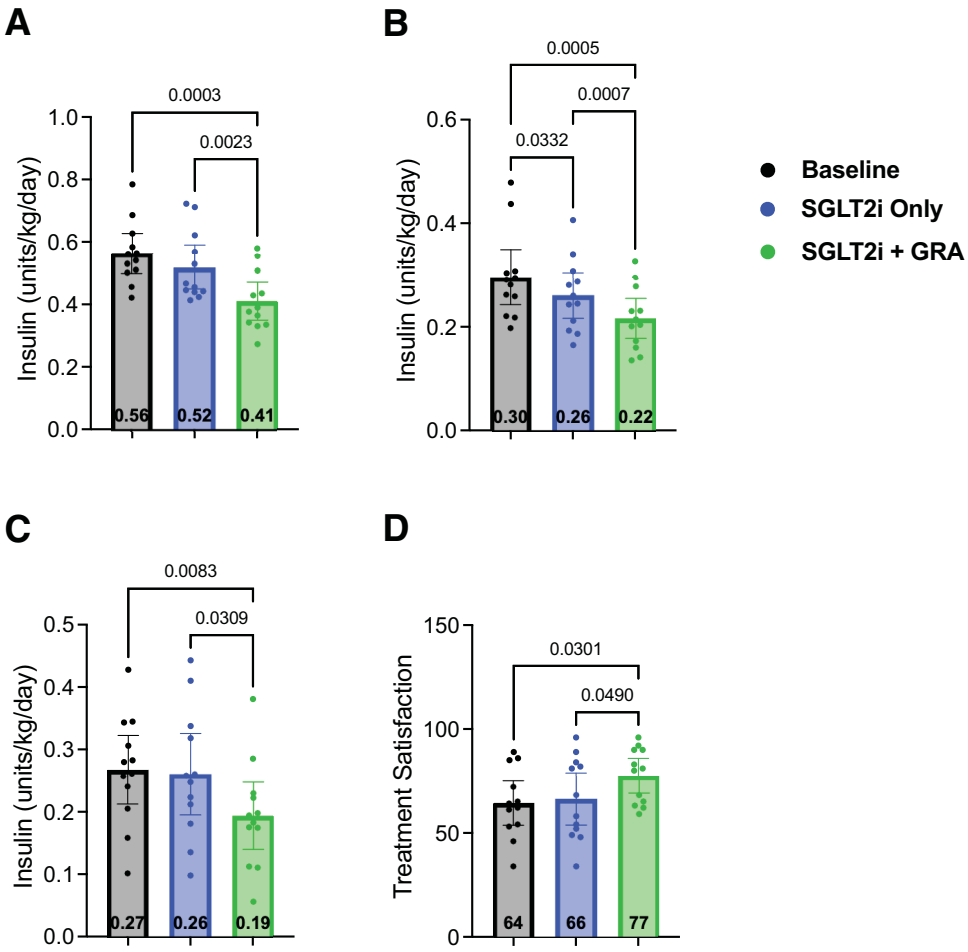

Figure 2—Average total daily insulin dose (*A*), average total daily basal dose (*B*), average total daily bolus dose (*C*), and scores from the DMSAT (*D*) are shown for Baseline, SGLT2 inhibitor + placebo, and SGLT2 inhibitor + GRA testing periods. Data are summarized as means and 95% CIs. Mean values, represented with columns, are also annotated at the bottom of each column. Dots depict individual values for each participant. Significant *P* values, determined with multiple comparisons tests, are indicated above brackets.

peak BHB concentration by the termination time of the IWT: IKet = (peak $BHB_{mmol/L}/T_{min}$) * 10^4. Mean IKet was higher with SGLT2 inhibitor treatment (73) than with combination therapy (46; P = 0.01). The IKet from the Baseline IWT (58) was midway between—and not significantly different from—that of the other testing periods.

Adjunctive Therapy Is Safe and Well Tolerated

Additional safety outcomes included blood pressure (BP), weight, cholesterol, results of hepatic laboratory tests, and occurrence of DKA or other ketosis events (i.e., elevated BHB without acidosis). Mean systolic BP was lower for the SGLT2 inhibitor testing period (114 mmHg) than for the combination SGLT2 inhibitor + GRA (126 mmHg; P = 0.02) and Baseline (125 mmHg; P = 0.04) testing periods. Mean diastolic BP was not significantly different in comparisons between Baseline (72 mmHg), SGLT2 inhibitor (66 mmHg), and combination SGLT2 inhibitor + GRA (72 mmHg) testing periods. Likewise, there was no difference in mean heart rate during Baseline (71 bmp), SGLT2 inhibitor (67 bpm), and combination SGLT2 inhibitor + GRA (70 bmp) testing periods. Mean body weight was 76.1 kg for Baseline, 75.1 kg for SGLT2 inhibitor therapy (P = 0.03 vs. Baseline), and 75.4 kg for combination SGLT2 inhibitor + GRA therapy. There were no differences between testing periods in mean total cholesterol or LDL cholesterol. Mean HDL was higher with combination SGLT2 inhibitor + GRA therapy (67 mg/dL) than with SGLT2 inhibitor therapy alone (61 mg/dL; P = 0.03). Mean AST and ALT concentrations increased during combination SGLT2 inhibitor + GRA therapy (29 and 27 units/L, respectively) and returned to baseline levels (19 and 18 units/L) by the end-of-study safety visit. There were no significant changes in bilirubin or alkaline phosphatase and no episodes of DKA or other ketosis events (BHB >1.0 mmol/L) outside the controlled IWT.

CONCLUSIONS

In our trial with 12 adult participants with type 1 diabetes, we investigated the effects of 4 weeks of insulin-adjunctive therapy using an SGLT2 inhibitor (dapagliflozin 10 mg daily) versus combination SGLT2 inhibitor + GRA (volagidemab 70 mg weekly), with a randomized, double-blind, crossover design. The study included comparison of outcomes for three testing periods: Baseline (insulin-only therapy), SGLT2 inhibitor (SGLT2 inhibitor + placebo), and combination SGLT2 inhibitor + GRA. Our primary hypothesis, that blocking glucagon action would enhance glycemic control and reduce ketogenesis

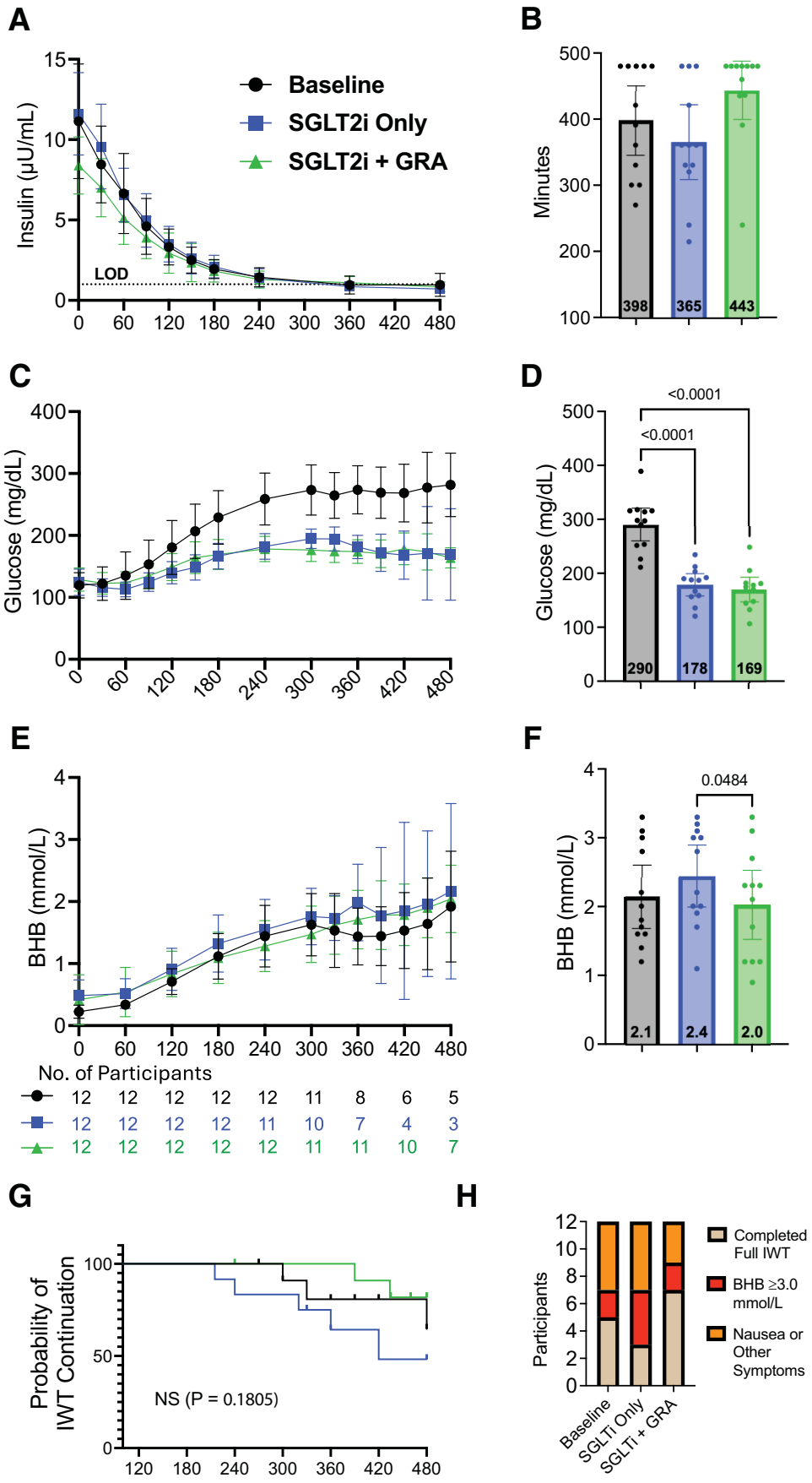

Figure 3—IWT. *A–F*: Serum insulin concentrations during the IWT (limit of detection of serum insulin [LOD]) (*A*), termination time (duration) of IWT (*B*), plasma glucose concentrations during IWT (*C*), peak plasma glucose achieved during IWT (*D*), BHB concentrations during IWT and number of

when added to SGLT2 inhibitor therapy, was confirmed. Blocking glucagon led to significant improvements in metabolic control, decreasing average glucose by ~20 mg/dL and increasing absolute percent time in target range by 16%, without increasing hypoglycemia. Additionally, combination therapy reduced total insulin requirements by 27% and reduced peak BHB during periods of insulinopenia. These outcomes underscore glucagon's critical role in type 1 diabetes metabolism and the potential of blocking glucagon action, which could facilitate the safe use of SGLT2 inhibitors.

CGM metrics showed improved glycemic control across a number of parameters including average glucose, glucose variability (SD), percent time in target glucose range, and percent time above target glucose range, with progressive improvement with escalating adjunctive therapy (Baseline vs. SGLT2 inhibitor vs. combination SGLT2 inhibitor + GRA). Compared with Baseline, combination SGLT2 + GRA therapy reduced average glucose by 19 mg/dL (estimated HbA_{1c} reduction, −0.7% [−15.8 mmol/mol]) and increased percent time in target range by 16% (>3.8 h per day). These significant improvements occurred even though all participants entered the study using HCL automated insulin delivery systems and the cohort had good blood glucose values at baseline (median HbA_{1c} 6.7% [50 mmol/mol] and mean time in target range 70%). Importantly, improvements in CGM metrics also occurred without an increase in hypoglycemic events. However, the efficacy of pharmacologic glucagon as a rescue therapy for severe hypoglycemia in the context of glucagon blockade (GRA therapy) remains a critical unanswered question. This topic is currently under investigation in our ongoing clinical trial (clinical trial reg. no. NCT06272695, ClinicalTrials.gov).

Combination SGLT2 inhibitor + GRA therapy was associated with increased patient-reported diabetes medication treatment acceptability and satisfaction in comparison with Baseline and SGLT2 inhibitor therapy alone. There were no detectable differences in diabetes emotional distress or mental well-being between the testing periods, though overall diabetes emotional distress was low and mental well-being was high at baseline.

The study results demonstrate that adjunctive therapy could reduce insulin dosing requirements while maintaining or improving glycemic control. This finding is particularly important given the nonphysiological distribution of exogenously delivered insulin in type 1 diabetes. Because peripherally injected insulin bypasses first-pass liver metabolism, basal insulin concentrations are ~2.5-fold greater in people with type 1 diabetes than in people without diabetes (18,19). This iatrogenic hyperinsulinemia, in turn, induces insulin resistance (19), which is pervasive in type 1 diabetes (18,20,21). Because insulin dosing plays a direct role in determining circulating insulin concentrations, adjunctive therapies that reduce insulin use would be expected to mitigate hyperinsulinemia and potentially improve insulin resistance. In this study, average total daily insulin use was 27% lower with combination SGLT2 inhibitor + GRA therapy than at Baseline and 21% lower versus SGLT2 inhibitor therapy. Reductions in insulin use occurred for both total daily basal and total daily bolus insulin. Mean basal serum insulin concentrations (collected before the start of each IWT) were ~30% lower for combination SGLT2 inhibitor + GRA than for Baseline or SGLT2 inhibitor alone.

During the IWT, peak plasma glucose and BHB concentrations were significantly lower with combination therapy, illustrating its potential in moderating DKA risks associated with SGLT2 inhibitor use. Peak plasma glucose during IWT was ~40% lower with SGLT2 inhibitor and combination SGLT2 inhibitor + GRA therapy than during Baseline testing. The maintenance of near-normal blood glucose concentrations despite insulinopenia illustrates the potential risk of euglycemic DKA that has been associated with SGLT2 inhibitor use (22). Fasting concentrations of BHB prior to IWT were higher for SGLT2 inhibitor and combination SGLT2 inhibitor + GRA therapy than for Baseline. However, peak BHB concentrations were 17% lower with combination SGLT2 inhibitor + GRA than with SGLT2 inhibitor alone (P = 0.048). This occurred even though the mean time to termination (duration) of the IWT was 18% shorter with SGLT2 inhibitor than with combination SGLT2 inhibitor + GRA (365 vs. 443 min). Thus, the rate of increase in BHB was greater during the SGLT2 inhibitor testing period (mean IKet 73) than during the combination SGLT2 inhibitor + GRA testing period (mean IKet 46; P = 0.01).

In terms of safety, there were no episodes of DKA or other ketosis events (BHB >1.0 mmol/L) outside of the controlled IWT. Consistent with previously published clinical trials in type 1 diabetes (23), BP was lower during the SGLT2 inhibitor testing period. BP during combination SGLT2 inhibitor + GRA therapy was similar to BP at Baseline, suggesting that the BP-lowering action of the SGLT2 inhibitor offset the effects of the GRA medication, which increased systolic and diastolic BP in our previous type 1 diabetes phase 2 trial (14). Likewise, the weight loss effect of the SGLT2 inhibitor (average −1.0 kg; P = 0.03 vs. Baseline), was attenuated when it was used in combination with the GRA (average −0.7 kg; not significantly different from Baseline). Thus, while GRA therapy may mitigate the risk of DKA that is associated with SGLT2 inhibition, it may also diminish some of the benefits (e.g., BP lowering and weight loss). Ultimately, further research will be needed to understand the net benefits—including cardiovascular and renal benefits—of combination adjunctive therapy.

In the previous phase 2 trial, GRA treatment led to elevated liver transaminases—similar to those seen with combination SGLT2 inhibitor + GRA therapy in the current study—and increased LDL cholesterol, which was not replicated here. In the current study, there were no significant elevations in bilirubin or alkaline phosphatase (signs of severe drug-induced liver injury). It has been hypothesized that elevations

participants remaining in IWT at each time point (*E*), and peak BHB achieved during IWT (*F*) are shown for Baseline, SGLT2 inhibitor + placebo, and SGLT2 inhibitor + GRA testing periods. Data are summarized as means and 95% CIs. For bar graphs (*B*, *D*, and *F*), mean values, represented with columns, are also annotated at the bottom of each column; dots depict individual values for each participant; and significant *P* values, determined with multiple comparisons tests, are indicated above brackets. *G* and *H*: Kaplan-Meier curve demonstrating IWT termination due to elevated BHB (≥3.0 mmol/L) (*G*) and reason for IWT termination during each testing period (*H*). *A*, *C*, *E*, and *G*: *x*-axis represents time elapsed (minutes) during IWT.

in liver transaminases associated with GRA therapy in type 1 diabetes may reflect a physiologic adaptation in response to changes in amino acid metabolism (14). However, development of a different GRA (the small-molecule GRA LY2409021) was abandoned when it was found to increase aminotransferases and hepatic fat in participants with type 2 diabetes (24). Further research, including assessment of liver fat, will be needed to understand the etiology of liver transaminase elevations associated with the GRA volagidemab in type 1 diabetes.

Limitations of the study include a modest sample size (n = 12) and a moderate treatment duration (4 weeks for each treatment with a 6-week washout period). Strengths of the study include a 100% retention rate; the randomized, double-blind, placebo-controlled trial design; and the crossover format, which removes interparticipant variability and increases the power to detect differences between treatments. All participants used HCL automated insulin delivery systems, the gold standard therapy for most people living with type 1 diabetes (25), prior to and during the trial. We view this as a strength of the study, though outcomes could have been different had we enrolled participants using multiple daily injection insulin therapy or continuous subcutaneous insulin infusion without HCL technology.

In conclusion, our study demonstrates the potential of combination SGLT2 inhibitor + GRA therapy as an effective adjunct to insulin in type 1 diabetes. This approach not only improves glycemic control and reduces insulin dosing but also suggests a means to minimize the risk of DKA associated with SGLT2 inhibitor use. Our findings highlight the significant therapeutic benefits and patient acceptability of this combination treatment in managing type 1 diabetes.

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