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BRIEF REPORT

Effect of a glucagon receptor antibody (REMD-477) in type 1 diabetes: A randomized controlled trial

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The aim of the current study (Clinical trial reg. no. NCT02715193, clinicaltrials.gov) was to study the efficacy and safety of REMD-477, a glucagon receptor antagonist, in type 1 diabetes. This was a randomized controlled trial in which 21 patients with type 1 diabetes were enrolled. Glycaemic control and insulin use were evaluated in outpatient and inpatient settings, before and after a single 70-mg dose of REMD-477 (half-life 7-10 days) or placebo. Inpatient insulin use was 26% (95% CI, 47%, 4%) lower 1 day after dosing with REMD-477 than with placebo (P = .02). Continuous glucose monitoring during post-treatment days 6 to 12 showed that average daily glucose was 27 mg/dL lower (P < .001), percent time-in-target-range (70-180 mg/dL) was ~25% greater (~3.5 h/d) (P = .001), and percent time-in-hyperglycaemic-range (> 180 mg/dL) was ~40% lower (~4 h/d) (P = .001) in the REMD-477 group than in the placebo group, without a difference in percent time-in-hypoglycaemic-range (<70 mg/dL). No serious adverse events were reported. Glucagon receptor antagonism decreases insulin requirements and improves glycaemic control in patients with type 1 diabetes.

KEYWORDS
diabetes, glucose homeostasis, glycaemic control, insulin

1 | INTRODUCTION

Type 1 diabetes is caused by an immune-mediated destruction of insulin-producing pancreatic β-cells, making patients completely dependent on exogenous insulin for survival. However, therapy with insulin, insulin analogues and insulin pumps cannot match the β-cell's regulated control of insulin release. Therefore, most patients with type 1 diabetes do not achieve the recommended goal for glycaemic control,[1] and often experience large swings in blood glucose concentrations and iatrogenic hypoglycaemia.[2,3]

The absence of insulin secretion from β-cells in patients with type 1 diabetes affects the paracrine regulation of juxtaposed α-cells,[4] which causes an increase in basal glucagon secretion and a paradoxical increase in the glucagon response to postprandial hyperglycaemia.[5,6] These increases in plasma glucagon stimulate hepatic glucose production and complicate glycaemic control.[7,8] The importance of glucagon in the pathophysiology of type 1 diabetes has been demonstrated in rodent models, which have shown that total β-cell destruction fails to induce diabetes in glucagon receptor knockout mice,[4] and glucagon receptor blockade normalizes plasma glucose without exogenous insulin in streptozotocin-induced diabetes.[9]

The purpose of the present study was to evaluate the therapeutic potential of glucagon blockade in patients with type 1 diabetes by conducting a proof-of-concept, randomized, double-blind, placebo-controlled trial to assess the effect of REMD 477, a human IgG2 monoclonal antibody against the human glucagon receptor, on insulin requirements and glycaemic control.

2 | METHODS

Twenty-one men and women with type 1 diabetes were randomized to either REMD 477 (n = 10) or placebo (n = 11) (Table S1). Eligibility

criteria included: age, 18 to 60 years; BMI, 18.5 to 30.0 kg/m^2; treatment with insulin infusion pump; C-peptide <0.2 ng/mL; HbA1c ≥ 6.0% and <9.0%; absence of severe hypoglycaemic events within the last 6 months; and serum alanine aminotransferase (ALT) < 1.5 × the upper limit of normal. All participants provided informed consent before participating in this study.

All participants monitored their blood glucose concentrations using CGM (DexCom G4, Dexcom, San Diego, California) and their insulin use for 2 weeks before the intervention to assess baseline glycaemic control. Participants were then admitted to the Clinical Research Unit (CRU) for 5 days. Meals composed of 50% calories as carbohydrate, 35% as fat and 15% as protein were provided at 8 AM, 1 PM and 6 PM, as well as a snack at 9 PM to ensure total daily energy requirements, calculated as 1.3 times the estimated resting energy expenditure.[10] Plasma glucose was monitored every 1 to 2 hours throughout admission, and targeted blood glucose concentrations (90-120 mg/dL postabsorptive and <180 mg/dL up to 2 hours postprandial) were maintained by intravenous insulin infusion. After the 24-hour baseline evaluation, insulin infusion was decreased to allow plasma glucose to increase to 250 to 300 mg/dL for 16 hours (from 12 AM on day 1 until 4 PM on day 2) to decrease the effect of intra-islet insulin concentrations on glucagon secretion. At 8 AM on day 2, participants received a subcutaneous injection of placebo or REMD-477 (70 mg; REMD Biotherapeutics, Camarillo, California). This dose (~1 mg/kg) was chosen because it was shown to decrease fasting blood glucose without adverse effects in a study conducted in healthy volunteers (unpublished observations). After discharge, participants were seen weekly for 8 weeks for medical monitoring, review of CGM data and adjustment of insulin therapy to obtain optimal glycaemic control.

The primary outcome was the effect of a single dose of REMD-477, which has a 7 to 10 day half-life, on 24-hour insulin requirements during inpatient day 4 compared with day 1. Secondary outcomes were the effects of REMD-477 on the percent of time CGM glucose was in target-range (70-180 mg/dL), hyperglycaemic-range (>180 mg/dL) and hypoglycaemic-range (<70 mg/dL), on daily average CGM glucose, and on 24-hour insulin use. Safety and tolerability, including changes in standard blood tests, lipid profile, liver biochemistries, and serum amylase, lipase and glucagon, were assessed.

Differences in outcome measures between the REMD-477 treatment and placebo were evaluated using repeated measures analysis of covariance with treatment as the fixed effect (REMD-477 vs placebo), study day fitted as a repeated measure as the within-subject effect, and the pre-treatment values as covariate. Model assumptions were reviewed prior to fitting. The least squares means for either treatment on each study day, along with their difference (REMD-477 – placebo), 95% confidence interval and *P* values were evaluated. It was estimated that 8 subjects in each group would be sufficient to detect a 30% reduction in insulin requirements with a power of 0.9 and an alpha value of 0.05. Therefore, a minimum of 10 subjects were recruited in each group to account for an estimated 20% drop-out rate.

3 | RESULTS

No participant withdrew from the study or missed any study visits. The amount of insulin needed to maintain plasma glucose targets on inpatient day 4 (24-48 hours after treatment with REMD-477 or placebo), compared with the amount needed on inpatient day 1 (baseline), decreased by 14% (7.3 units) in the REMD-477 group, but increased by 12% (4.8 units) in the placebo group (*P* = .02) (Figure 1A). During post-treatment days 6–12, average daily CGM glucose concentration was 27 mg/dL lower (95% CI, 15, 40; *P* < .001), without a significant difference in daily insulin dose (Figure 1B). The percent time-in-target range (70-180 mg/dL) was ~25% greater (~3.5 h/d) (*P* = .001), and the percent time-in-hyperglycaemic range (>180 mg/dL) was ~40% lower (~4 h/d) (*P* = .001) in the REMD-477 group than in the placebo group (Figure 1C). Percent time-in-hypoglycaemic range (<70 mg/dL) during post-treatment days 6 to 12 did not differ from baseline and did not differ between groups (Figure 1C).

The most common AEs in the REMD-477 group were headaches and oropharyngeal pain that resolved without treatment within 2 and 8 days, respectively (Table S2). Mean serum ALT increased, but remained within the normal range in the REMD-477 group, and did not increase above twice the upper limit of normal in any subject at any

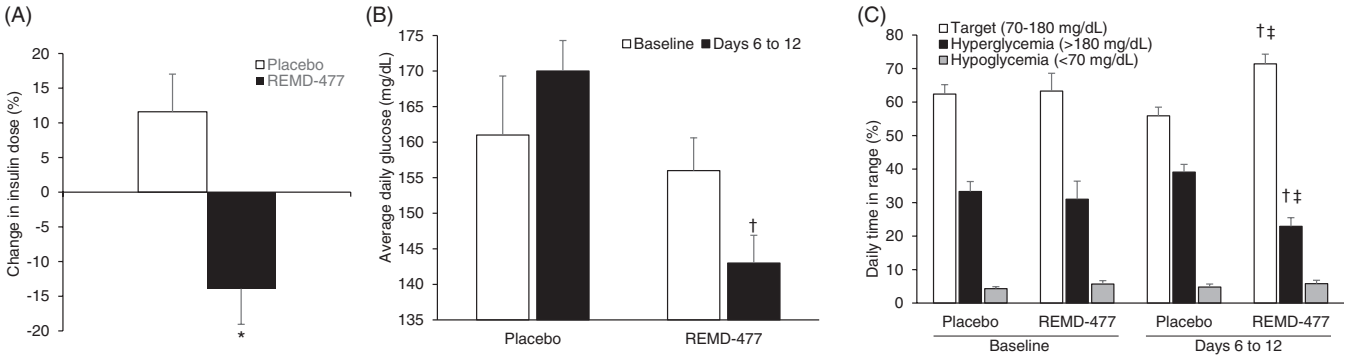

FIGURE 1 A, Percent change in insulin use 1 day after treatment with REMD-477 (black bar) or placebo (white bar) (Day 4) relative to baseline (Day 1) during the inpatient study. B, Average daily glucose concentration, assessed by continuous glucose monitoring (CGM), during a 2-week outpatient baseline (white bars) and at Days 6–12 (black bars) after treatment with REMD-477 or placebo. C, Percent time CGM glucose in target (70–180 mg/dL) (white bars), hyperglycaemic (> 180 mg/dL) (black bars) and hypoglyceamic (< 70 mg/dL) (gray bars) ranges during a 2-week outpatient baseline and during post-treatment at Days 6 to 12. Value significantly different from placebo value, $^*P = .021$, $^\dagger P < .001$. Value significantly different from baseline value, $^\ddagger P = .001$. Data are presented as LS means ± SE

time point. Fasting plasma glucagon increased from 20.2 to 56.3 pmol/L, 2 weeks after REMD-477 treatment (P = .01) and returned to baseline by 8 weeks. No changes in body weight, blood pressure, heart rate or plasma lipid profile were detected in either group.

4 | CONCLUSIONS

This proof-of-concept, randomized, placebo-controlled trial evaluated the effect of REMD-477, a human IgG2 monoclonal antibody against the human glucagon receptor, on insulin requirements and glycaemic control in patients with type 1 diabetes. We found that a single dose of REMD-477 decreased insulin requirements and improved glycaemic control, without an increase in hypoglycaemia or adverse events. These data support the notion that glucagon is involved in the pathophysiology of type 1 diabetes, and demonstrate the potential of glucagon receptor blockade as a novel therapeutic approach for this patient population.

A series of studies have evaluated the effect of glucagon receptor blockade in humans by using small molecule antagonists, antisense oligonucleotide inhibitors of the glucagon receptor and monoclonal glucagon receptor antibodies.[11] All of these approaches have consistently improved glycaemic control, manifested by a decrease in A1c and blood glucose concentrations. However, several adverse effects of therapy have also been reported, including an increase in blood pressure, weight, plasma LDL-cholesterol and plasma transaminase concentrations.[11] While not measured with other compounds, a recent publication showed an increase in hepatic fat content with LY2409021, which was the first to correlate the transaminase increase with potential, underlying pathophysiology.[12] An additional concern is that chronic glucagon receptor blockade will cause pancreatic α-cell hyperplasia, which has been shown in animal models[13,14] and in case reports demonstrating α-cell hypertrophy and severe hyperglucagonaemia, without evidence of glucagonoma syndrome, in individuals with loss-of-function glucagon receptor mutations.[14,15] Our study is the only one published, that we are aware of, that assesses the use of glucagon receptor blockade in individuals with type 1 diabetes, and it is possible that adverse effects with glucagon antagonism will differ between type 1 and type 2 diabetes. However, the type 1 population has a unique need for additional therapies, given that they are completely dependent on exogenous insulin, often experience large swings in blood glucose and often have inadequate overall glycaemic control. Although we did not detect any serious adverse effects of REMD-477 therapy in our participants, the design of our study, which involved only a single injection of drug, is not able to adequately evaluate potential side effects of long-term therapy.

The results of the present study demonstrate the potential efficacy of glucagon receptor blockade as an adjunctive therapy in patients with type 1 diabetes. Additional studies are needed to determine the optimal dose and dosing schedule for maximum insulin-sparing and glucoregulatory effects, while fully evaluating the adverse effects of long-term therapy.

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Conflict of interest

J. P., D. R., R. H., R. U. and S. K. are receiving research support from REMD Biotherapeutics for other studies. S. K. and J. P. have served as consultants to REMD Biotherapeutics. None of the other authors has any conflicts of interest relevant to this manuscript.

Author contributions

All authors assisted in study implementation. Dr Klein and Dr Pettus assisted in study design and manuscript preparation. Dr Unger and Dr Henry assisted in study design.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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