Concomitant oral and subcutaneous insulin therapy toward stabilization of uncontrolled Type 1 Diabetes Mellitus (T1DM)

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BACKGROUND

Uncontrolled hepatic gluconeogenesis is suggested to play a central role in unstable T1DM. Restoration of normal portal insulin/glucagon ratios may enable tighter regulation of gluconeogenesis and glucogenolysis. Orally administered insulin is speculated to induce similar effects, while offering the benefit of hepatic first-pass insulin metabolism, reduced systemic exposure and ease-of-use.

OBJECTIVE

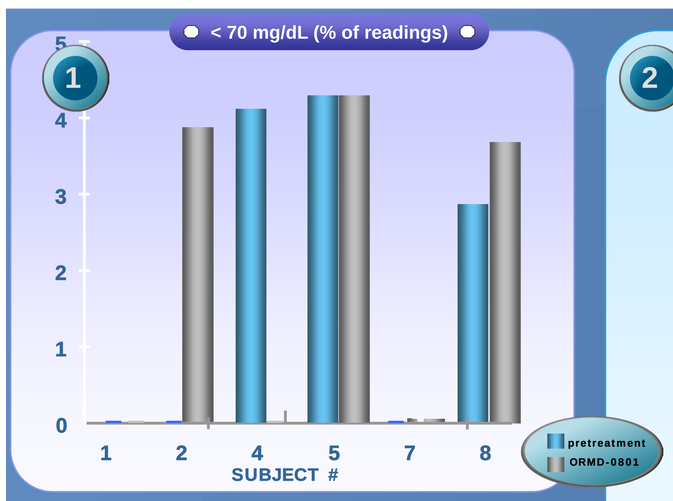
To assess the safety and impact of an orally delivered insulin in combination with standard patient insulin therapy, on the stability of glycemic readings in uncontrolled T1DM patients.

METHODS

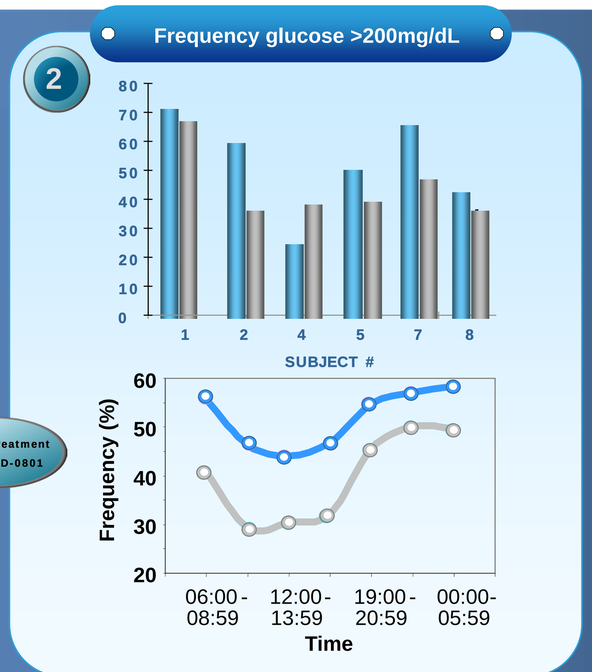
- STUDY: Phase 2a, single-blind, open-label, single-center
- SETTING: Home-based
- PARTICIPANTS: 8 male or female volunteers, ages 27-50, diagnosed by attending physician with uncontrolled T1DM, with HbA1c values ranging between 7.5% and 11%, on multiple or continuous daily doses of subcutaneously administered insulin.
- DESIGN: Baseline blood glucose profiles were recorded with a blinded continuous glucose monitoring device (Medtronic, Northridge, CA) for a period of five days. Patients were then instructed to continue with their usual insulin regimen, while adding ORMD-0801 to their daily regimen three times daily, 45 min before meals, for a period of ten days. During this phase, glucose profiles continued to be monitored by the blinding glucose monitoring device.

RESULTS

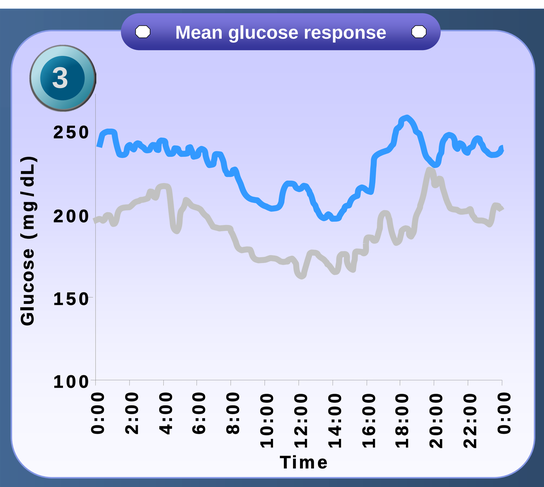
No adverse events were reported throughout the 15-day study period. Oral insulin support yielded more frequent blood glucose recordings below 70 mg/dL, when compared to the pretreatment phase (Figure 1; 1.99±0.88% versus 0.45±0.2%, respectively; p=0.06). In parallel, the frequency of glucose readings >200 mg/dL was 24.4% lower upon addition of ORMD-0801 to the treatment regimen (Figure 2; p=0.026). ORMD-0801 treatment led to a 16.6% decrease in glucose area under the curve values, with the largest reductions (21.2%) measured between 5-7 PM (Figure 3).



(1) Frequency of blood glucose concentrations <70 mg/dL throughout the pretreatment (blue) versus the ORMD-0801, oral insulin-treatment (gray) phases.



(2) Frequency of blood glucose concentrations >200 mg/dL throughout the pretreatment (blue) versus the ORMD-0801, oral insulin-treatment (gray) phases.



(3) Mean glucose concentrations before (blue) and during (gray) ORMD-0801 oral insulin support therapy. Mean glucose levels of six T1DM subjects are presented.

CONCLUSIONS

Concomitant administration of orally and subcutaneously delivered insulins was safe and well tolerated by the participating uncontrolled T1DM patients. Moreover, the recorded glucose profiles suggest that ORMD-0801 can stabilize blood glucose concentrations, with a most prominent effect during evening hours. Future studies will be required to assess translation of this therapy into reduced levels of HbA1c, and of risks associated with uncontrolled T1DM.

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