Preprandial Oral Insulin (ORMD-0801) Reduces Rapid-Acting Insulin Requirements and Fasting Glucose Levels in T1DM Patients

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BACKGROUND

Systemically administered insulin is the mainstay of insulin-dependent anti-diabetes regimens but is associated with risk of hypoglycemia and weight gain. Portally infused insulin brings to a more rapid and pronounced suppression of hepatic glucose production, reduced fasting blood glucose concentrations and to reduced circulating peripheral insulin levels. Similarly, oral insulin (ORMD-0801), deposited directly into the portal vein following its release from enteric-coated capsules in the gastrointestinal tract, has been shown to reduce fasting and prandial glucose excursions in diabetes patients and to minimize glucose instability when provided as an adjunct to subcutaneous insulin regimens in T1DM patients.

OBJECTIVES

- To evaluate the change in bolus insulin requirements in T1DM patients preprandially treated with ORMD-0801, in comparison to baseline and in comparison to placebo
- To determine the pharmacodynamic effect of ORMD-0801 on fasting blood glucose concentrations
- To evaluate the safety and tolerability of ORMD-0801

DESIGN

In this randomized, double-blind, placebo-controlled, prospective study, 25 adult T1DM patients were outfitted with a blinded continuous glucose monitor (CGM). During the 3-day in-patient run-in period, patients were treated with placebo capsules (3 times daily, 45 min before meals) and baseline patient insulin requirements were recorded and averaged. A fresh CGM cannula was then fitted for the following 7-day in-patient treatment period, during which, patients were dosed 3 times daily, 45 min before meals, with either ORMD-0801 (8 mg insulin) or placebo capsules. Study staff administered insulin according to the patient's sliding scale, with adjustments made, as necessary.

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STUDY CONDUCT AND PATIENT DEMOGRAPHICS

	Placebo	ORMD-0801
N	10	15
Completed study	10	15
Completed run-in	10	15
Received all 21 doses	10	15
Age (yrs± SD)	37.6 ± 9.6	38.9 ± 11.9
Male	5	12*
Female	5	3
White	10	13
Black/African Am	0	1
Asian	0	1

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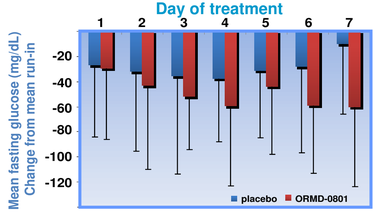

Mean fasting glucose concentrations. Morning fasting fingerstick glucose measurements were performed and are presented as the mean change from baseline glucose levels. Error bars represent standard deviation.

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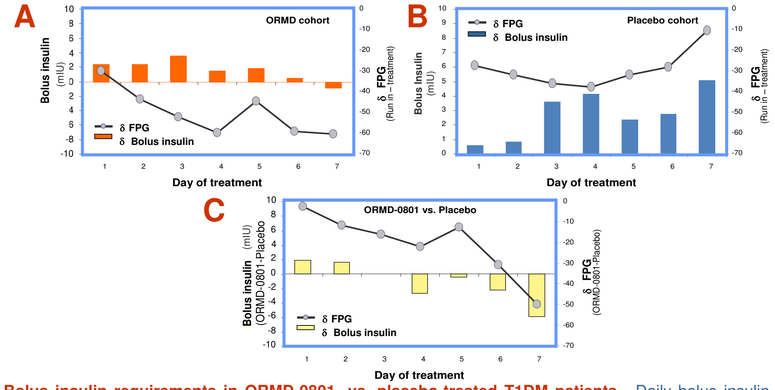

Bolus insulin requirements in ORMD-0801- vs. placebo-treated T1DM patients. Daily bolus insulin requirements were recorded throughout the 7-day treatment period and compared to requirements recorded in the run-in period for ORMD-0801 (A) and placebo-treated (B) patients. Mean bolus insulin requirements of the two cohorts were also compared (C).

RESULTS

Ten patients were treated with placebo capsules, while 15 received ORMD-0801 treatment. There were significantly more male patients in the active treatment group, but mean patient age was similar between cohorts (Fig 1). Fasting plasma glucose (FPG) levels were consistently lower than baseline on all treatment days among ORMD-0801-treated patients, dropping to -60.2±63.3 mg/dL below baseline values on day 7. Placebo-treated patients demonstrated smaller reductions in FPG readings, with a mean -10.2±55.7 mg/dL drop from baseline measured on day 7 of treatment (Fig 2). Change from baseline bolus insulin requirements on days 4-7 of the study were markedly different between the two treatment cohorts (Fig 3A vs. 3B), where rapid-acting insulin requirements were below baseline requirements by day 7 of ORMD-0801 treatment, while placebo-treated patients required 5.07 mIU more insulin than at baseline. A mean difference of -5.9 mIU insulin intake between active versus placebo-treated patients was recorded on day 7 (Fig 3). On day 7 of treatment, an equal number of hypoglycemic events (<60 mg/dL) requiring clinical intervention was reported for each cohort (n=12 per cohort).

CONCLUSIONS

Overall, preprandial ORMD-0801 treatment reduced the short-acting insulin demands required to maintain euglycemia in T1DM patients. In parallel, the active treatment led to a greater drop in FPG concentrations, when compared to placebo treatment, seemingly due to improved hepatic insulinization and subsequently normalized gluconeogenesis/glycogenolysis ratios. In addition, ORMD-0801 proved safe and well tolerated at the tested regimen.

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