ORAL INSULIN-INDUCED REDUCTION IN LIVER FAT CONTENT IN T2DM PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS

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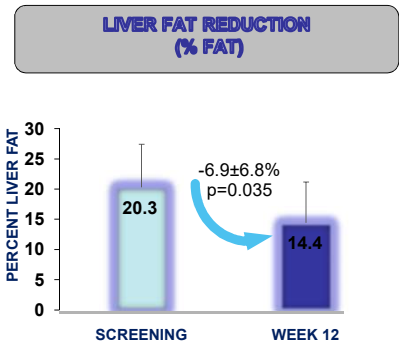
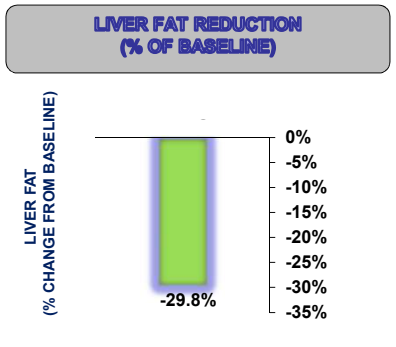
BACKGROUND

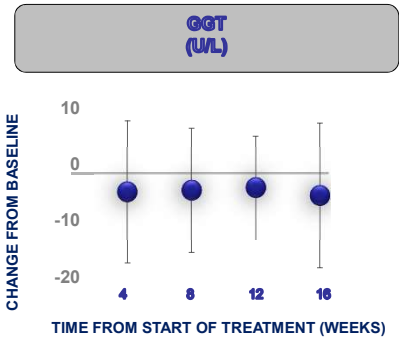
Nonalcoholic fatty liver disease (NAFLD) and subsequent nonalcoholic steatohepatitis (NASH) are leading causes of chronic liver disease, with disease progression directly associated with insulin resistance (IR) and affects up to 70% of T2DM patients. No safe and effective treatments are currently available and management is primarily non-pharmacological. The IR component common to both NAFLD/NASH have raised proposal for direct insulin intervention for T2DM patients with NAFLD. Recently, salient metabolic effects of oral insulin have been suggested, owing to first pass metabolism and local insulin availability and concentration in liver fat cells. Such a formulation would be particularly advantageous in the case of NAFLD/NASH-T2DM.

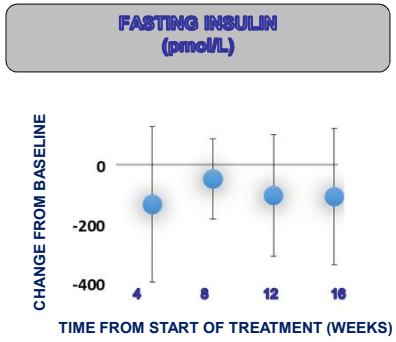
OBJECTIVES

- To assess the safety, tolerability of an oral insulin formulation (ORMD-0801) in T2DM patients with NASH
- To assess the early effects of ORMD-0801 on liver fat in T2DM patients with NASH









CONCLUSIONS

These preliminary observations suggest a palliative effect of oral insulin on NASH in T2DM patients, as shown by reductions in liver fat content and in in chronic hepatitis marker. These encouraging findings will require further validation in large-scale, randomized clinical trials.

DESIGN AND METHODS

In this open-label, pilot study, 8 adult T2DM patients with NASH, with a BMI ≥25, hepatic steatosis >8% by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and CAP FibroScan ≥238 dB/m, liver enzyme abnormalities ULN≤5 times, fibrosis score 2≤F≤3 and HbA1c ≤8.5%, were subjected to a 2-week placebo run-in phase. Thereafter, ORMD (2x8 mg capsules) was preprandially administered once-daily for 12 consecutive weeks. Study visits were performed after 1, 2, 4, 8 and 12 weeks of treatment, at which fasting blood glucose and insulin levels were determined, fasting blood glucose diaries were reviewed, standard blood chemistry tests were performed and a Fibroscan test and MRI-PDFF assessment were conducted to determine fat liver content.

RESULTS

The patient population included 5 males and 3 females, of an average age of 51.8 ±11.9 years and a BMI of 32.8 ±6.0 kg/m2. All had T2DM and NASH. The 12-week ORMD-0801 treatment proved safe and tolerable in all patients, with no serious or severe adverse events recorded throughout the study period. The 12-week treatment induced a mean -6.9±6.8% reduction in liver fat content (sign test p value: 0.035), as measured by MRI-PDFF. In parallel, concentrations of gamma-glutamyltransferase (GGTP), a key marker of chronic hepatitis, were significantly lower after 12 weeks of treatment as compared to baseline (-14.6±13.1 U/L; sign test p value: 0.008), as were fasting insulin levels (-96.5±206.0 pmol/L; sign test p value: 0.035)

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