Effects of Leucine-Metformin Combinations on Glycemic Control in Type 2 Diabetes

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Session Sunday General Poster Session
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Category Clinical Therapeutics/New Technology–Oral Agents

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We previously showed leucine (Leu) to activate Sirt1 signaling and amplify the effects of metformin (Met), resulting in Leu-Met synergy in preclinical studies. We have now conducted a phase 2A study to test the efficacy of Leu-Met combinations versus standard Met in patients with type 2 diabetes. Following a 4 week washout from monotherapy, 96 patients were randomized into 4 study arms: 2.2 g Leu/250 mg Met/day, 2.2 g Leu/500 mg Met, 2.2 g Leu/1000 mg Met or 1700 mg Met (active control) for 28 days. All treatments were well tolerated with similar adverse events reported. Meal tolerance tests (MTT) were conducted at treatment days 0 and 28 to assess total and incremental area under the glucose curve (AUC). Additional outcomes included fasting plasma glucose and insulin, HbA1c and 24-hour glucose via continuous glucose monitoring (CGM). The mid- and high doses of Leu-Met dose-responsively improved all measures of glycemic control, while the lowest dose did not. The Met control arm exhibited greater improvements in fasting glucose ($p<0.05$), average daily glucose ($p<0.05$) and total, but not incremental, glucose AUC (p=NS) in the *per protocol* cohort, while the intention-to-treat (ITT) cohort showed comparable glucose improvements between Leu-Met and Met control. Notably, the Met control arm exhibited markedly greater improvements in glucose and glucodynamics than expected from previous reports. The Met control arm had an ~two-fold greater loss of glycemic control during washout ($p<0.05$) resulting in poorer baseline control and a larger potential improvement with treatment compared to the other arms. Adjusting for this difference resulted in comparable effects of Leu-Met and Met control. Further, a responder analysis of fasting glucose and CGM showed equivalence in both responder fraction (65%) and magnitude of effect between the 2.2g Leu/1000 mg Met arm and the 1700 mg Met control arm. These data suggest that leucine can augment the effectiveness of Met to enable a significant (~40%) Met dose reduction in man.

Keywords Metformin, Leucine

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