Effect of fecal microbiota transplantation on CYP3A activity in patients with systemic sclerosis

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Background: Studies suggest that the gut microbiota may influence the expression and activity of cytochrome P450 3A (CYP3A). The gut microbiota composition in patients with systemic sclerosis (SSc) seems to differ from healthy individuals. Fecal microbiota transplantation (FMT) may change the gut microbiota composition further and lead to alterations in CYP3A activity. The primary objective was to investigate the effects of FMT on CYP3A activity in patients with SSc using midazolam as a probe drug. Secondarily, we aimed to study potential microbiome-derived midazolam metabolism *in vitro*.

Methods: In this substudy of a randomized, placebo-controlled trial, SSc patients with gastrointestinal symptoms received FMT with Anaerobic Cultivated Human Intestinal Microbiome (ACHIM) or placebo at weeks 0 and 2. At week 12, all patients received ACHIM. Pharmacokinetic investigations (8-hr) were conducted at the 3 study visits with 1.5 mg oral midazolam followed by an intravenous dose (2.5–7.5 mg) two hours later. A population pharmacokinetic model was used to determine pharmacokinetic parameters, and linear mixed effects models to determine mean difference and 95% confidence interval (CI) of the pharmacokinetic parameters from week 0 to weeks 2 and 12. Fecal midazolam metabolism was assessed in ACHIM lysates, prepared by bead beating and sonication, then incubated (37°C) with midazolam. Samples were collected over 48-hr to determine *in vitro* depletion rate of midazolam.

Results: Twenty-two patients (57±12 years) were included in the substudy, and 18 patients (10 and 8 in the ACHIM and placebo group, respectively) supplied pharmacokinetic profiles at all visits. There was no change in absolute bioavailability at week 2 (1.6% [95% CI: -12, 15]) or week 12 (0.25% [95% CI: -14, 15]) in the ACHIM group. Similarly, there was no change in clearance at weeks 2 and 12. No significant differences were found between the groups at any visits. There was a negligible effect on midazolam concentrations in ACHIM lysates after 48-hr incubation.

Conclusions: Absolute bioavailability and clearance of midazolam in patients with SSc did not change after FMT, suggesting unaltered CYP3A activity. No direct microbiome-derived metabolism of midazolam was observed in ACHIM lysates.

Key words: cytochrome P450 3A, fecal microbiota transplantation, systemic sclerosis