Thematic trial: phase 2 dose-ranging randomized clinical trial of capsular or enema fecal microbiota transplant to prevent hepatic encephalopathy in cirrhosis already on Rifaximin and Lactulose


Background and Aims: Patients with cirrhosis and hepatic encephalopathy (HE) already on lactulose and rifaximin have few options to prevent further HE. Fecal microbiota transplant (FMT) was helpful in small studies, but route/dosage remains unclear. Aim: to compare 2 FMT routes (oral capsule & enema) with dose-ranging in HE prevention.

Method: A double-blind, placebo controlled RCT with 2 modes of FMT administration in cirrhosis pts on lactulose & rifaximin was completed under FDA IND. 4 groups (Gp1: both oral+enema active, Gp2: oral active+placebo enema, Gp3: oral placebo+active enema, Gp4: both oral+enema placebo) received oral+enema FMT at baseline & a 3rd oral dose at day30. 2 donors were used for FMT products. Pts with recent infections, other antibiotics, MELD>22, transplant & immunosuppression were excluded. We needed 60 total (15/gp) for >90% power across gps at 6 mths on ITT analysis. The primary outcome was safety, especially HE recurrence defined as ≥Grade 2 on West-Haven criteria. Secondary outcomes were other adverse events, changes in infections/cirrhosis severity/cognition (PHES/Stroop) & patient-reported outcomes (Sickness Impact Profile (SIP), total/physical/psych; high=worse). Regression for HE-recurrence was performed.

Results: 60 pts (15 per group) with similar MELD (13,12,12,12, p=0.5) & age (65,63,61,63, p=0.6) on lactulose+rifaximin were included. Last prior HE episode duration was similar (8-13 mths prior, p=0.51). Baseline cognition, SIP, & cirrhosis severity were similar between gps.

Course: All were followed till death or 6 mths in-person/remotely. 6 pts dropped out (2 Gp1 patients died after falls in rehab), 1 Gp2 died after a seizure), 1 Gp2 & 2 Gp 4 did not return for visits), but ITT analysis was performed. 2 pts in Gp 2 & 1 in Gp 1 did not receive the day30 active dose. 5 pts missed some visits due to COVID-19, but were seen remotely. 4 pts developed infections (SBP, cholecystitis & 2 cellulitis), all unrelated to FMT.

Primary outcome: HE recurrence was highest in Gp 4 (both placebo: 40%) vs other (Gp 1:13%, Gp 2:13%, Gp3.0%, p=0.03). Both Gp 1 pts who died had HE prior to death.

Secondary outcomes: liver-related hospitalizations tended higher in Gp 4 vs rest (47% vs Gps 1-3: 7-20%, p=0.12). MELD/PHES/Stroop did not change, but SIP total/physical & psych improved with FMT (p=0.003) on RMANOVA. Regression in all pts: HE recurrence was related to dose number (OR 0.27, 95% CI 0.10-0.79, p=0.02), male sex (OR 0.16, 0.03-0.89, p=0.04) & Physical SIP (OR 1.05, 1.01-1.10, p=0.05). Dose/route/donor: Within FMT recipients neither dose, route, nor FMT donor affected HE recurrence.

Conclusion: HE recurrence was significantly lower in FMT (enema or oral capsule) recipients versus placebo in a phase 2 placebo-controlled, double-blind, dose-ranging RCT in pts with cirrhosis and HE on lactulose and rifaximin. The FMT route, donor, and dose range did not affect HE recurrence.