14 CLINICAL STUDIES

14.2 HIV-associated Enteropathy

In a small open label study, patients who had severe HIV-associated enteropathy with approximately 5-6 watery stools per day, SBI 2.5 g BID for 8 weeks aided in improving their symptoms and quality of life. Median peripheral blood CD4+ T-cell count was 372 cells/mL (193, 459) at baseline, was unchanged at 339 cells/mL (210, 468) after 8 weeks and 348 cells/mL (225, 397) after 48 weeks. Median bowel movements/day decreased from 5.7 (range: 5, 8.4) to 2 (2, 3.8) ($p = 0.013$) and stool consistency [1-constipated to 6-watery] decreased from a median of 5.3 (5, 6) to 3 (2.2, 3.8) ($p = 0.013$) at 8 weeks. For those five who continued SBI to week 48, durable bowel movements/day, stool consistency and questionnaire responses were reported at 2 (2, 3), 2.5 (1, 3.8), and 0.5 (0, 5.5), respectively. Median GI symptoms questionnaire scores (cramping, urgency, incontinence, and nocturnal diarrhea [0 to 24 with normal < 2]) decreased from 6 (5, 11) to 0.5 (0, 5.5) ($p = 0.013$) at 8 weeks. Increased gastrointestinal absorption assessed by D-xylose and urinary excretion increased in 7/8 subjects over the course of the 8-week intervention from a median of 33.8 mg (28.7, 38.2) at baseline to 40.9 mg (19.8, 44.4) at week 7 ($p = 0.19$). These 7 patients demonstrated SBI was well-tolerated, with a reduction in HIV-associated enteropathy as noted by a decrease in stool frequency, stool consistency and GI symptoms. Immunohistochemistry enumeration of absolute lamina propria CD3+/CD4+ T-cell density revealed an increase from 213 to 322 cells/mm^2 ($p = 0.016$) (a median increase of 140 cells/mm^2) after 8 weeks of SBI (normal values 836 cells/mm^2). By contrast, previous studies showed increases of 57 cells/mm^2 (IQR: −9.0, 82) after 9 months of antiretroviral therapy. While the lamina propria CD3$^+$/CD8$^+$ density was unchanged (502 cells/mm^2 and 598 cells/mm^2 at baseline and week 8, respectively), the lamina propria CD4$^+$/CD8$^+$ ratio increased from 0.41 to 0.62 ($p = 0.016$). MCP-1 levels were unchanged at week 8 but decreased in 5/5 subjects at week 48 (379.5 ng/mL [225, 502]) ($p = 0.06$). Intestinal fatty acid-binding protein initially rose in 7/8 subjects after 8 weeks from 3514 ng/mL (2858, 4275) to 4042 ng/mL (3233, 5613) ($p = 0.039$) and then fell below baseline in 4 of the 5 who continued receiving SBI to 2442 ng/mL after 48 weeks (1267, 2875) ($p = 0.12$). These data suggest that an initial period of increased growth and possibly repair was followed by lowered steady state levels of enterocyte turnover/damage relative to baseline. MMP-9/TIMP-1 ratios in subjects were significant lower than controls at baseline (0.13 [0.07, 0.33] versus 0.42 [0.23, 0.44] [$p = 0.007$]), respectively and then tended to increase at the EOT to 0.33 (0.13, 0.73) ($p = 0.08$). MCP-1 levels were negatively correlated to CD3$^+$/CD4$^+$ lamina propria density ($r = -0.59$, $p = 0.019$) with all time points examined together, suggesting that MCP-1 expression is associated with mucosal immunologic damage. Similarly, MMP-9/TIMP-1 ratios were negatively correlated with CD3+/CD8+ lamina propria density ($r = -0.70$, $p = 0.0039$) suggesting that factors promoting CD8+ T-cell infiltration into the lamina propria correlate with impaired collagen kinetics. Baseline serum I-FABP levels were negatively correlated with subsequent rise in lamina propria CD4+ T-lymphocytes ($r = -0.74$, $p = 0.046$). Log10 absolute 16S rDNA stool quantification was unchanged between baseline and week 8 [7.125 cp/g (6.34, 7.5) to 7.415 cp/g (6.4, 7.56)]. In addition, SBI has demonstrated an effect on the composition of the gut microbiota in patients with HIV-associated enteropathy. Pro-inflammatory gammaproteobacteria tended to decrease from 0.70% to 0.12%. *Clostridium* (genus) and *Ruminococcus* (also a genus in the *Clostridia* family) decreased from 6.5 (2.80, 10.65) to 3.4 (2.50, 5.89) and 0.89 (0.52, 1.29) to 0.30 (0.15, 0.47), respectively. *Ruminococcus* decreased in all eight subjects. Decreases in *Clostridium* in the stool and correlated with duodenal CD3+/CD4+ density ($r = -0.63$; $p < 0.01$). Changes in gut microbiota correlated with local lymphocyte populations that increased significantly with short-term SBI. A total of 20 AEs were reported by 6 subjects. Most of the reported AEs were mild (7/20) or moderate (9/20) in severity, and judged by the investigator to be not related to study medication (16/20). The 4 events judged to be severe included worsening diarrhea, worsening diarrhea (due to ova/parasites), worsening lower back pain, and groin pain. Thirteen (13) of the AEs were reported as resolved, while 5 were not resolved at the end of the study and the outcome of 2 AEs was unknown. The most common AEs included worsening or recurrence of diarrhea (5 AEs reported by 4 subjects), constipation (2 subjects), and worsening neuropathy (3 AEs reported by 2 subjects). Adverse events that were reported by 1 subject each

included sinus infection, throat infection, gastroesophageal reflux disease, flatulence, worsening lower back pain, groin pain, nausea, bronchitis, acute ear infection, and infection on finger.