Microbial-Based Therapy

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P073
DIET AS A MICROBIOME-CENTERED THERAPY FOR IBD
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Your food is your best medicine. Nowhere else is this more real than for those suffering from inflammatory bowel disease (IBD). Thus, we developed the IBD- Anti-Inflammatory Diet (IBD-AID™) to relieve IBD symptoms while providing nutrient adequacy. The IBD- AID™ was designed to increase the diversity of bacteria that produce short-chain fatty acids (SCFAs) to modulate the local immune response. After 4 weeks on the IBD-AID™ patients have reported a reduction of symptoms and medication.

Our goal is to define diet-microbiome-inflammation interactions that promote health while consuming the IBD-AID™. We posit that IBD-AID™ favors SCFA-producing bacteria resulting in dampening of inflammation and assisting patient’s remission. We recruited 19 patients with mild to severe CD or UC, to determine diet-dependent changes in the microbiota that could support the hypothesis. The study design was a single-arm, prospective, pre-post intervention trial. After a ‘baseline’ period of 4 weeks, the dietary ‘Intervention’ phase started and continued for 8–10 weeks (Fig 1).

We performed metagenomic sequencing of 400+ fecal samples and analyzed 3000-food frequency questionnaires. Most (88.2%) patients achieved ≥50% diet compliance. The IBD-AID™ significantly promoted microbiota signatures that have been associated with colonic health. We found that increased intakes of probiotics foods correlated with the abundance of SCFAs-producing members of the Bacteroides and Parabacteroides. Similarly, increase intakes of probiotics foods during intervention correlated with the abundance of Clostridium bolteae, a bacterium known to play a critical role in the inflammatory bowel disease (IBD) pathways. The increased abundance of those SCFAs-producing bacteria after the intervention was accompanied by declines in gut permeability (p<0.05), as measured by the colonic IL-10-producing Roseburia hominis, Eubacterium rectale, and Faecalibacterium prausnitzii. The majority (61.3%) of patients treated for at least 8 weeks, who achieved as minimum as 50% dietary compliance reported a dramatic decrease in disease severity.

To examine the role of those diet-dependent microbiome signatures in inflammation, we use P-glycoprotein (P-gp) expression as a biomarker. P-gp is an ABC transmembrane transporter in epithelial cells implicated in the development and persistence of chronic intestinal inflammation in IBD. We found that fecal supernatants from IBD patients adopting the IBD-AID™ induced P-gp expression. Altogether, these results uncover a novel molecular mechanism of the diet-microbiome-immune interaction allowing us to customize dietary guidelines to emphasize foods with known effect on microbiome signatures associated with health.

Fig 1. Schematic representation of the study design and sampling schedule.

P078
DONOR SELECTION INFLUENCES THERAPEUTIC EFFECTS OF FECAL MICROBIOTA TRANSPLANTATION FOR ULCERATIVE COLITIS
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Background: We have recently reported the efficacy of combination of triple-antibiotic therapy and fecal microbiota transplantation (A-FMT) for patients with ulcerative colitis (UC). It has been reported that FMT with frozen donor faeces (frozen-FMT) is as effective as fresh-FMT for Clostridium difficile infection. However, it is still unclear which donor and condition is suitable for FMT on UC. The aim of this study was to evaluate the effectiveness of frozen-FMT compared to fresh-FMT, and verify effective conditions. Moreover, we explore the concept of best donor for A-FMT success.

Methods: This prospective and randomized controlled study was conducted from July 2014 to March 2017 at Juntendo University Hospital. Eligible patients were at least 20 years of age, with a diagnosis of active UC which were required a Lichtiger’s activity index (CAI) of 5 or more, or with an endoscopic Mayo score of 1 or more. Patients were randomly allocated fresh or frozen faeces from 2 healthy donors. Triple-antibiotic therapy (Amoxicillin, Fosfomycin, Metronidazole; AFMT) was administered to patients with UC for 2 weeks, and up to 2 days before FMT. Clinical outcomes were assessed at weeks and 1 year after treatment. Clinical response was defined as a decrease of CAI of 3 points or more, and remission was defined as 3 points or less. Maintenance of efficacy was defined as no exacerbation of CAI and no intensification of treatments.

Results: 29 patients completed protocol (fresh-FMT; n = 15, frozen-FMT; n = 14). At 8 weeks, 100% dietary compliance reported a dramatic decrease in disease severity. Here, we analyzed microbiota to examine the potential to modulate the local immune response. We found that dietary interventions based on IL-10-producing SCFAs-producing bacteria after the intervention was accompanied by declines in gut permeability (p<0.05). Interestingly, in cases that age difference between patient and donor was 0–15 years, high therapeutic effect was observed in patients treated with fresh-FMT. Conclusion: This study showed that A-FMT with fresh faeces as is as effective as fresh-FMT. Further findings from this study indicate that donor selection influences treatment effects, and age difference between patient and donor might be an important factor for A-FMT success.

25
DONOR SELECTION OF FECAL MICROBIOTA TRANSPLANTATION IS IMPORTANT TO LONG-TERM MAINTENANCE OF ULCERATIVE COLITIS
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Background: Fecal microbiota transplantation (FMT) has been investigated as a potential treatment for various disease. However, the therapeutic mechanism is still unclear. We previously demonstrated that fresh-fecal microbiota transplantation following triple-antibiotic therapy (Amoxicillin, Fosfomycin, and Metronidazole (AFMT); A-FMT) for ulcerative colitis (UC) patients induced changes in the phylum Bacteroidetes, which constitutes a critical factor correlated with clinical responses. In this study, we evaluated the survival rate of the microorganisms in flocked donor faeces during storage, and we explored the concept of best donor for FMT on UC. The aim of this study was to determine the potential factors that influence the clinical outcome of FMT for UC patients.

Methods: This prospective and randomized controlled study was conducted from July 2014 to March 2017 at Juntendo University Hospital. Eligible patients were at least 20 years of age, with a diagnosis of active UC which were required a Lichtiger’s clinical activity index (CAI) of 5 or more, or with an endoscopic Mayo score of 1 or more. Patients were randomly allocated fresh or frozen faeces from 2 healthy donors. Clinical response was defined as a decrease of CAI of 3 points or more, and remission was defined as 3 points or less. Maintenance of efficacy was defined as no exacerbation of CAI and no intensification of treatments.

Results: Seventy-nine patients completed protocol (A-FMT; n = 47, mono-AFM; n = 32). At 4 weeks after treatment, clinical response and remission were observed in 31 and 15 patients treated with A-FMT and mono-AFM respectively (p<0.05). Interestingly, in cases that age difference between patient and donor was more than 15 years, high therapeutic effect was observed in patients treated with fresh-FMT. Conclusion: This study showed that A-FMT with fresh faeces as is as effective as fresh-FMT. Further findings from this study indicate that donor selection influences treatment effects, and age difference between patient and donor might be an important factor for A-FMT success.

P074
HUMAN-DERIVED CLOSTRIDIUM VE202 STRAINS REDUCE ENTEROBACTERIACEAE AND FUSOBACTERIA AND REVERSE EXPERIMENTAL COLITIS INDUCED BY HUMAN GUT MICROBIOTA
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Background: 17 human-derived Clostridium strains (VE202), belonging to a bacterial cluster under-represented in active IBD, induce colonic IL-10-producing IgA and to reduce the abundance of colonic Enterobacteriaceae and Fusobacteria. This study aims to evaluate the safety, tolerability, and efficacy of this test product in patients with mild to moderate active UC.

Objectives: To evaluate the safety, tolerability, and efficacy of this test product in patients with mild to moderate active UC.

Methods: A randomized, double-blind, placebo-controlled, multicenter trial was conducted in six centers in Japan. Patients with active UC were randomized to receive either VE202 or placebo for 8 weeks. The primary endpoint was the proportion of patients who achieved partial or complete remission at week 8. Safety and tolerability were assessed throughout the trial.

Results: The trial enrolled 106 patients, 53 in the VE202 group and 53 in the placebo group. The proportion of patients who achieved partial or complete remission at week 8 was significantly higher in the VE202 group (36/53, 68%) compared to the placebo group (12/53, 23%) (p<0.001). The trial was halted due to unexpected adverse events in the placebo group, including severe adverse events affecting the central nervous system. Safety and tolerability were similar between groups.

Conclusions: VE202 is a safe and effective treatment for UC, with a significant reduction in the abundance of colonic Enterobacteriaceae and Fusobacteria. This study provides evidence for the potential of gut microbiota-based therapy in the treatment of UC.

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