

Long-term Multidonor Fecal Microbiota Transfer (FMT) by Oral Capsules for Active Ulcerative Colitis

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Short title: Oral Capsule-based Long-term Multidonor FMT for Active UC

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To the Editors,

We read with great interest the article by Sood A. et al. entitled 'Role of Fecal Microbiota Transplantation for Maintenance of Remission in Patients with Ulcerative Colitis: A Pilot Study' which highlight the role of long-term fecal microbiota transfer (FMT) in maintenance of a stable clinical remission in ulcerative colitis (UC) patients.¹ Their results support latest studies on FMT showing that the long-term application have crucial benefits in the therapy of UC.² Furthermore, in *Clostridioides difficile* infection (CDI), the use of oral fecal microbiota capsules resulted in comparable responses to that achieved by endoscopic approaches, which simplifies long-term administration while obviating invasive procedures.³

Consequently, we aim to investigate intestinal microbiome normalization, clinical response and safety during capsule-based long-term multidonor FMT in active UC.

Ten patients (8M, 37±7 years; 50% pancolitis, 25% left-side colitis, 25% proctosigmoiditis; 80% were on corticosteroids, 7/10 patients were biologic experienced) with active UC (Partial Mayo Score ≥4 with Mayo Endoscopic Subscore ≥1 despite treatment with corticosteroids (<30mg prednisone/day), immunosuppressive, and/or TNF/integrin antibody) were treated with vancomycin (4x125 mg/d) and metronidazole (2x400 mg/d) and underwent FMT (2x5 capsules per day for 5 consecutive days for 12 weeks).

Stool from donors (n=5) was homogenized, double-encapsulated and stored at –80°C as described.⁴ Multidonor FMT was performed by application of different donor batches.

Two patients developed serious adverse events (worsening colitis with increased stool rate) and stopped capsule intake after 5 days. Otherwise, no side effects occurred except mild complaints within the first week (bloating and flatulence).

Oral application of encapsulated microbiota rapidly increased microbial diversity, reaching values similar to those of single donors (Figure 1a) and engraftment was evidenced by an increase in the similarity of patient microbiota to that of the respective multidonor (Figure 1b).

Despite the rapid modulation of the microbiota, clinical improvement occurred slowly. The Partial Mayo Score improved in 7/8 patients (5.8 ± 1.7 to 2.6 ± 1.1) (Figure 1c). One patient achieved a steroid-free clinical remission with endoscopic proven mucosal healing and 5/8 patients showed an improvement of the Mayo Endoscopic Subscore (2.5 ± 0.5 to 1.5 ± 1.0) (Figure 1d). In summary, the total Mayo Score decreased under FMT therapy (8.3 ± 1.8 to 4.0 ± 1.8) (Figure 1e).

Our results, in conjunction with the original article, demonstrate that capsule-based long-term multidonor FMT is safe, highly effective in modulating microbial diversity and community structure and showed beneficial clinical responses in active UC. Our capsule-based FMT strategy simplifies long-term administration while obviating any invasive procedures, thus increasing safety and cost effectiveness. However, a multicenter randomized placebo controlled clinical trial with long-time examination (clinicaltrials.gov, NCT03843385) is necessary to provide more evidence on the efficacy of FMT for UC therapy.

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Author's contributions

A.S.: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval. M.V.: acquisition of data, analysis and interpretation of the data, drafting the article, final approval. P.G.: acquisition of data, revising the article, final approval. D.H.P.: acquisition of data, analysis and interpretation of the data, drafting and revising the article, final approval. A.S.: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval.

Conflict of Interest Statement

None of the authors have any conflict of interest in relation to publication of this work.

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Figure Legend

Figure. Capsule-based long-term multidonor FMT modulated fecal microbiota diversity and community structure and induced clinical improvement in UC patients. (a) Shannon diversity of single donor (n=17; green) and multidonor microbiota (n=8; dark green) used for FMT. Course of Shannon diversity (fecal microbiota) of 8 patients from baseline (red; day -14 before FMT) until day 28. Patients received antibiotics (yellow; day -1) and FMT (2x5 capsules per day for 5 days per week; day 1–28). Plot shows single values combined with box plot. Whiskers indicate min to max values. (b) Similarity of patient fecal microbiota to that of the multidonor during the experimental course. Plot shows data from 6 patients starting from baseline (full line) and 2 patients (dashed line) starting with antibiotics until day 28. (c) Partial Mayo Score. (d) UC stage based on endoscopic exploration (Mayo Endoscopic Subscore). Black line represent median. (e) Total Mayo Score. (c-e) Plots show data from baseline (day -14 before FMT) until week 12 (day 84; clinical endpoint) of 8 UC patients.

Figure



