Determining the optimal route of faecal microbiota transplant in patients with ulcerative colitis: the STOP-Colitis pilot RCT

Mohammed N Quraishi,[1] Catherine A Moakes,[2] Mehmet Yalchin,[3] Jonathan Segal,[3] Natalie J Ives,[2] Laura Magill,[2] Susan E Manzoor,[1] Konstantinos Gerasimidis,[4] Shrushma Loi,[2] Christel McMullan,[5] Jonathan Mathers,[5] Christopher Quince,[6] Manjinder Kaur,[2] Nicholas J Loman,[7] Naveen Sharma,[1] Peter Hawkey,[1] Victoria McCune,[8] Ben Nichols,[4] Vaios Svolos,[4] Caroline Kerbiriou,[4] Claire McMurray,[7] Andrew Beggs,[1] Richard Hansen,[9] Ailsa L Hart,[3] Daniel R Gaya[10] and Tariq H Iqbal[1*]

[1]University of Birmingham Microbiome Treatment Centre, Birmingham, UK
[2]Birmingham Clinical Trials Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[3]St Mark's Hospital, London, UK
[4]Human Nutrition, University of Glasgow, Glasgow, UK
[5]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[6]Organisms and Ecosystems, Earlham Institute, Norwich, UK
[7]Institute of Microbiology and Infection, University of Birmingham, Birmingham, UK
[8]South Tees NHS Foundation Trust, Middlesbrough, UK
[9]School of Medicine, University of Dundee, Dundee, UK
[10]Gastroenterology Unit, Glasgow Royal Infirmary, Glasgow, UK

[*]Corresponding author t.h.iqbal@bham.ac.uk

Disclaimer: This report contains transcripts of interviews conducted in the course of the research, or similar, and contains language which may offend some readers.

Published August 2024
DOI: 10.3310/YCJD4579

Scientific summary

Determining the optimal route of faecal microbiota transplant in patients with ulcerative colitis: the STOP-Colitis pilot RCT

Efficacy and Mechanism Evaluation 2024; Vol. 11: No. 14
DOI: 10.3310/YCJD4579

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Ulcerative colitis (UC) results from an exaggerated immune response to an imbalanced (dysbiotic) colonic microbiome in genetically predisposed patients. At the inception of this study, there had been four published randomised controlled trials (RCTs) comparing faecal microbiota transplantation (FMT) with placebo to treat UC in adults. Of these four seminal studies, three involved delivery of FMT via the colonic route and one a combination of delivery to the foregut and colon. This latter study was the only one of the four not to show a difference in efficacy compared to placebo. Foregut-delivered FMT is extensively and successfully used in clinical practice to treat *Clostridioides difficile* infection (CDI). From the results of the UC trials, FMT appeared to have therapeutic potential for UC. However, the methodology employed in these studies was varied and, taking into account the efficacy of FMT delivered to the foregut to treat CDI, there was uncertainty regarding the best route of delivery in the context of UC.

Objectives

The aims of this pilot study were as follows:

- to determine which FMT administration route [nasogastric (NG) or colonic (COLON)] should be investigated in a randomised double-blind, placebo-controlled trial
- to determine whether a full-scale RCT was feasible.

In order to achieve these aims, the pilot study had the following clinical objectives. To assess the following:

- whether FMT by the NG route induces clinical response in patients with active UC
- whether FMT by the COLON route induces clinical response in patients with active UC
- tolerability and safety
- which route of FMT delivery (if any) was suitable to investigate in a full-scale RCT.

The aims of the qualitative research were to assess the following:

- patient and clinician acceptability of FMT (NG route)
- patient and clinician acceptability of FMT (COLON route).

The aims of the nested-mechanistic substudy were to assess the following:

- whether FMT by either route is associated with a change in faecal calprotectin as a surrogate marker of colonic inflammation
- changes in the colonic microbiome induced by FMT via each route
- changes in the metabolome [short-chain fatty acids (SCFAs)] induced by FMT via each route
- effect of diet (donors)
- time from stool donation to treatment.

Copyright © 2024 Quraishi *et al.* This work was produced by Quraishi *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Methods

In this prospective, multicentre, open-label, parallel group, randomised pilot study, adult patients with mild to moderate active UC (partial Mayo score of ≥4 and ≤8) were recruited from three centres in the UK (Birmingham, Glasgow and St Mark's, London). Patients were randomised to receive FMT delivered either via a NG tube for delivery to the stomach (foregut-NG) on 4 consecutive days repeated after a month or by a combination of delivery through a colonoscope followed by 7 weekly enemas (hindgut-COLON). All participants underwent a treatment schedule using FMT derived, in each case, from a single donor.

The primary outcome was a composite assessment of both qualitative and quantitative data based on efficacy, acceptability and safety. Clinical response (primary measure of efficacy) was defined as a ≥3 point and a ≥30% reduction in full Mayo score from randomisation to week 8 and a ≥1 point reduction in the rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1. Patient and clinician acceptability of FMT and preference of treatment route was assessed through semi-structured qualitative research interviews. Interviews also explored reasons for adherence to treatment allocation and patients' perspectives on FMT and trial experience. Participants were interviewed face to face or by telephone at two time points, first following the screening visit and prior to randomisation, and second after the 12-week follow-up period. Safety was assessed by the number of participants experiencing adverse events (AEs) and serious adverse events (SAEs).

For the translational research, stool samples were taken from participants at baseline and then at 2 weekly intervals throughout the study to assess microbiome diversity (by 16S rRNA sequencing) and to examine the effect of FMT on faecal calprotectin. Donor stool samples were also analysed by 16S rRNA sequencing. Biopsy samples were taken from the colon at the time of endoscopy (baseline and week 8) to analyse mucosa-associated microbiome by 16S rRNA sequencing. SCFA levels in stool samples were also measured throughout the study and blood was taken from participants to look for changes in C-reactive protein (CRP) in response to FMT. Donors were asked to fill in a dietary questionnaire in order to look for associations between dietary components in their habitual diet and the efficacy of their donated FMT samples.

Results

Thirty patients with UC were randomised between March 2018 and April 2019; 16 to NG; 14 to COLON route. Seven participants in the NG arm and two participants in the colonic arm withdrew from the study. Clinical response was achieved in a higher proportion of participants in the colonic arm [9/12 (75%)] compared with the NG arm [2/8 (25%)]; [adjusted risk ratio 2.94 (95% confidence interval, 0.84 to 10.30)]. In the colonic arm, 12/14 (86%) participants were considered adherent compared with 8/16 (50%) in the NG arm. AEs were reported in 11/14 (79%) participants in the colonic arm and 11/16 (69%) in the NG arm. There were three SAEs in two participants in the NG arm, and none in the colonic arm.

Qualitative research found a high level of enthusiasm for the trial among both patients and staff. Patients were more positive about the colonic treatment route than the NG route, both before randomisation and after the patients had been through the study.

Lower calprotectin levels, implying reduced colonic inflammation, averaged over the last half of the treatment course (weeks 4, 6 and 8), were seen in the responders (N = 11, mean 508.6 mg/kg) versus the non-responders (N = 9, mean 853.6 mg/kg) (p = 0.03). Furthermore, there was a negative association between faecal microbiome alpha diversity [rarefied total operational taxonomic unit (OTU) richness] and calprotectin levels (p < 0.01). This is the first time that change in faecal calprotectin, a widely used clinical inflammatory biomarker in UC, has been reported in response to FMT in inflammatory bowel disease (IBD).

With respect to SCFAs, there were significant and large increases observed in the concentration of acetate (45% increase, $p = 0.05$) and butyrate (57% increase, $p = 0.03$) across all participants ($N = 19$) from baseline to week 2 following FMT treatment. This effect was also observed over the course of the entire FMT treatment period from baseline to 8 weeks ($N = 16$, acetate 21% increase, $p = 0.02$; butyrate 39% increase, $p = 0.08$). Significant changes were not observed for the other SCFAs measured, notably propionate (2 weeks $p = 0.46$, 8 weeks $p = 0.36$). The observed increase in acetate and butyrate was not associated with clinical response, and in fact when restricted to the responder group ($N = 9$) changes at both 2 and 8 weeks were no longer significant, although increases were still observed.

Across all participants that completed FMT to day 56, and for whom baseline and week 8 DNA was available ($N = 13$), there was no significant change in faecal microbiome alpha diversity, as measured by rarefied Shannon diversity of 3% OTUs ($p = 0.43$). However, when restricted to the colonic arm only ($N = 8$), there was a significant increase in alpha diversity ($p = 0.01$) observed after FMT. Again, for those participants in the colonic arm that responded to FMT, there was a significant increase in alpha diversity (rarefied Shannon diversity, $p < 0.01$) compared to those who did not. No differences were seen in alpha diversity of mucosa-associated bacteria pre and post treatment.

Donor microbiome diversity, as measured by rarefied 16S rRNA gene Shannon diversity, varied substantially between donors. There was a non-significant positive association between clinical response and donor diversity ($p = 0.19$) with the treatment arm taken into account.

In this pilot study, CRP values were lower at baseline in the colonic arm (4.2 mg/l) compared with the NG arm (11.3 mg/l). Similarly, CRP values at weeks 4, 6 and 8 were also lower in the colonic arm than in the NG arm.

With regard to data derived from diet questionnaires administered to donors, higher milk and milk product intakes were associated with higher alpha diversity, but this was not statistically significant.

The mean number of days from stool donation to FMT treatment was similar in participants who achieved a clinical response compared with those who did not achieve a clinical response. There was no association between time from stool donation and treatment, and clinical response when added to the primary intention-to-treat analysis model.

Conclusion

This pilot study suggests that in patients with active UC, FMT delivered via the colonic route appears to be safe and better tolerated with signals suggesting greater efficacy compared to the NG route. The pilot study was welcomed by patients and clinicians, and FMT appears, at least in the short term, to be safe and well tolerated. On review of these data, the Independent Oversight Committee recommended progressing to the planned placebo-controlled randomised trial, which would be powered to assess efficacy, and would have enabled more detailed mechanistic studies to assess for strains engrafting from donors to recipients, which are associated with clinical response.

Patients remain very interested in FMT as a potential treatment for UC as this microbiome manipulation affords an alternative therapy to immune system suppression as a means to treat UC. The trial management group involved in this pilot believe that further studies to assess the efficacy of FMT in UC with a focus on understanding mechanisms are warranted as the first step towards developing precision live biotherapeutics for IBD.

Copyright © 2024 Quraishi *et al.* This work was produced by Quraishi *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Trial registration

This trial is registered as ISRCTN74072945 and EudraCT 2015-005753-12.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (NIHR award ref: 13/179/01) and is published in full in *Efficacy and Mechanism Evaluation*; Vol. 11, No. 14. See the NIHR Funding and Awards website for further award information.

Efficacy and Mechanism Evaluation

ISSN 2050-4373 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

Efficacy and Mechanism Evaluation (EME) was launched in 2014 and is indexed by Europe PMC, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and NCBI Bookshelf.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme.

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal
Manuscripts are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme funds ambitious studies evaluating interventions that have the potential to make a step-change in the promotion of health, treatment of disease and improvement of rehabilitation or long-term care. Within these studies, EME supports research to improve the understanding of the mechanisms of both diseases and treatments.

The programme supports translational research into a wide range of new or repurposed interventions. These may include diagnostic or prognostic tests and decision-making tools, therapeutics or psychological treatments, medical devices, and public health initiatives delivered in the NHS.

The EME programme supports clinical trials and studies with other robust designs, which test the efficacy of interventions, and which may use clinical or well-validated surrogate outcomes. It only supports studies in humans and where there is adequate proof of concept. The programme encourages hypothesis-driven mechanistic studies, integrated within the efficacy study, that explore the mechanisms of action of the intervention or the disease, the cause of differing responses, or improve the understanding of adverse effects. It funds similar mechanistic studies linked to studies funded by any NIHR programme.

The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This article

The research reported in this issue of the journal was funded by the EME programme as award number 13/179/01. The contractual start date was in January 2015. The draft manuscript began editorial review in October 2022 and was accepted for publication in September 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, the EME programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the EME programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Copyright © 2024 Quraishi *et al.* This work was produced by Quraishi *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).