CLINICAL SCIENCE

Safety and efficacy of faecal microbiota transplantation for active peripheral psoriatic arthritis: an exploratory randomised placebo-controlled trial

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ABSTRACT

Objectives Although causality remains to be established, targeting dysbiosis of the intestinal microbiota by faecal microbiota transplantation (FMT) has been proposed as a novel treatment for inflammatory diseases. In this exploratory, proof-of-concept study, we evaluated the safety and efficacy of FMT in psoriatic arthritis (PsA).

Methods In this double-blind, parallel-group, placebo-controlled, superiority trial, we randomly allocated (1:1) adults with active peripheral PsA (≥3 swollen joints) despite ongoing treatment with methotrexate to one gastroscopic-guided FMT or sham transplantation into the duodenum. Safety was monitored throughout the trial. The primary efficacy endpoint was the proportion of participants experiencing treatment failure (ie, needing treatment intensification) through 26 weeks. Key secondary endpoints were change in Health Assessment Questionnaire Disability Index (HAQ-DI) and American College of Rheumatology (ACR20) response at week 26.

Results Of 97 screened, 31 (32%) underwent randomisation (15 allocated to FMT) and 30 (97%) completed the 26-week clinical evaluation. No serious adverse events were observed. Treatment failure occurred more frequently in the FMT group than in the sham group (9 (60%) vs 3 (19%); risk ratio, 3.20; 95% CI 1.06 to 9.62; p=0.018). Improvement in HAQ-DI differed between groups (0.07 vs 0.30) by 0.23 points (95% CI 0.02 to 0.44; p=0.031) in favour of sham. There was no difference in the proportion of ACR20 responders between groups (7 of 15 (47%) vs 8 of 16 (50%)).

Conclusions In this first preliminary, interventional randomised controlled trial of FMT in immune-mediated arthritis, we did not observe any serious adverse events. Overall, FMT appeared to be inferior to sham in treating active peripheral PsA.

Trial registration number NCT03058900.

Key messages

What is already known about this subject?
► Psoriatic arthritis (PsA) is a systemic immune-mediated disease associated with subclinical gut inflammation and dysbiosis of the intestinal microbiota.
► Faecal microbiota transplantation (FMT) has demonstrated local therapeutic immune-modulating abilities in patients with chronic inflammatory bowel disease.

What does this study add?
► In this first preliminary, randomised controlled trial of FMT in immune-mediated arthritis, transfer of donor microbiota was safe, but appeared inferior to sham in reducing disease activity in patients with active peripheral PsA concomitantly treated with methotrexate.

How might this impact on clinical practice or future developments?
► Whether microbial dysbiosis or specific bacteria are common or decisive mediators of disease activity in PsA and whether this proposed relation can be modified without exacerbating the disease will be crucial to clarify to determine the future role of microbiota-targeted interventions in the management of PsA.

immune-mediated arthritic disease.[2] Recently, this theory has gained renewed interest due to accumulating evidence of disease-related imbalance (dysbiosis) in the composition and function of the intestinal microbiota in chronic disorders.[3–5] Among these, psoriatic arthritis (PsA)[6] has been associated with decreased intestinal bacterial diversity, displaying both disease-specific patterns[7] and microbial abnormalities similar to those seen in other subtypes of spondyloarthritis, rheumatoid arthritis and inflammatory bowel disease (IBD).[8] These findings have encouraged research into the host–microbiota interplay in the dysregulated

INTRODUCTION

For a century, the link between enteric infections and reactive arthritis[1] has motivated investigation into the proposed gut–joint axis implicating intestinal micro-organisms in the aetiology of

immunological cascade underlying immune-mediated arthritis and the prospects of microbiota-targeted therapies.[9]

Faecal microbiota transplantation (FMT) is currently considered the most efficient method to restore a healthy diversity of the gastrointestinal microbiota.[10 11] Indeed, the transfer of faeces containing minimally manipulated communities of micro-organisms from a donor to a recipient has revolutionised the treatment of *Clostridioides difficile* infection.[12] FMT may also induce beneficial responses in patients with IBD, thereby demonstrating local therapeutic immune-modulating abilities.[13] However, whether manipulation of the intestinal microbiota can treat extraintestinal, immune-mediated disorders remains to be established.[14] This is the first exploratory, randomised trial to assess the safety and efficacy of FMT in patients with active, peripheral PsA.

METHODS

Trial design

This is a proof-of-concept, 26-week, 1:1 randomised, parallel-group, double-blind, placebo-controlled, single-centre superiority trial. In 2015, the Regional Committees on Health Research Ethics for Southern Denmark (DK-S-20150080) and the Danish Data Protection Agency (15/41684) approved the trial protocol (see online supplemental appendices S1 and S1A). Although not required by the Danish Health and Medicines Authority, we fulfilled the requirements of documentation, monitoring and reporting according to the principles of Good Clinical Practice. We registered the trial with ClinicalTrials.gov. Our trial protocol paper was published in 2018.[15] The study was conducted at one Danish tertiary referral hospital with nationwide inclusion. All participants gave written informed consent. The trial was temporarily suspended from March to May 2020 due to the COVID-19 pandemic (see online supplemental appendix S4). A statistical analysis plan (see online supplemental appendix S2) was developed with subsequent closure (2 April 2020) before unmasking and analysis (10 June 2020).

Participants

We included adults who were between 18 and 75 years of age, fulfilled the Classification for Psoriatic Arthritis criteria,[16] and had active peripheral disease, defined as three or more swollen joints, despite ongoing treatment with methotrexate at the maximal tolerable dose (≥15 mg/week) for at least 3 months prior to study inclusion. A washout period of 12 weeks (26 weeks for biologic agents) was required in patients previously treated with intra-articular or systemic glucocorticoids, and non-methotrexate conventional synthetic and biologic disease-modifying antirheumatic drugs. Key exclusion criteria were immune-mediated arthritis other than PsA, IBD, cancer, severe chronic infection, and history of food allergy, severe food intolerance or coeliac disease.[15]

Donor selection and stool preparation

The transplants were obtained from four healthy stool donors recruited from a non-profit, public stool bank located at the local blood and tissue transplant service.[17] Every step of the donation process and the laboratory handling were in agreement with the requirements of the European Union's regulative directives on human cells and tissues (2004/23/EC). Donors did not receive any compensation and had to pass an extensive screening programme (see online supplemental table S3) before and after the 30-day donation cycle.[15] Stool donations were transported to the stool bank facility within 1 hour after

defaecation in an airtight container placed in a cooling bag. The donation was processed at normal room temperature within 2 hours of delivery under aerobic conditions, including 10–15 s of blending, before storage at −80°C (median storage time: 20 months; range: 2.5–30).[18]

Interventions

The transplant consisted of a single stool donation (50 g) mixed with saline (0.9%) and glycerol (10%) to a total volume of 250 mL. Before transplantation, we thawed the material to 36°C. The sham transplant consisted of 250 mL saline (0.9%) mixed with three drops of food colouring (E150c). We performed the allocated treatment within 14 days of the baseline visit. Treatment preparation included a 6-hour fast and one dose of oral proton-pump inhibitor. The transplant suspension was transferred into the third part of the duodenum via a closed system of tubes under gastroscopic guidance.

Outcomes

Safety was monitored by open assessment of adverse events (AEs) and evaluated before unmasking. The National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 was used to grade the severity.[19] We evaluated causality for expected AEs of grade 2 and above and for all unexpected AEs regardless of severity. The primary efficacy endpoint was a composite outcome on the proportion of participants who experienced treatment failure through 26 weeks, defined as need for at least one of the following: more than one intra-articular glucocorticoid injection, and non-methotrexate conventional synthetic and/or biologic disease-modifying antirheumatic drugs. This endpoint covered disease activity and shared decision-making between the patient and the rheumatologist in accordance with the European PsA recommendations.[20] Three key secondary endpoints were evaluated at week 26: change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI),[21] proportion of participants fulfilling the American College of Rheumatology (ACR20) response[22] and change from baseline in the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index.[23] Additional secondary outcomes addressed all essential domains in the PsA core outcome set[24] (see table 1).

Randomisation and masking

We assigned participants to FMT or sham transplantation using permuted blocks with varying sizes of four and six, according to computer-generated random numbers. These lists were generated by the trial statistician and uploaded to a concealed area of a password-protected trial database (REDCap[25]) by an independent and otherwise trial agnostic data manager.[15] The trial coordinator implemented the randomisation. The randomisation record and the signed transfusion journals were stored in the database with restricted access separate from the patient record and other study data so the participants and the treating rheumatologists (ie, care providers and outcome assessors) remained unaware of treatment allocation and treatment.

Sample size and power considerations

Conceptually guided by the idea that at least twice as many participants in the sham group would be treatment failures, compared with the FMT group if the procedure should potentially be considered clinically relevant, we wanted to randomly assign 80 patients with PsA to two groups (40 patients to each), providing a good statistical power (90%) to detect a difference

Table 1 Comparison of efficacy endpoints at week 26

Endpoint	FMT (n=15)	Sham (n=16)	Difference between groups (95% CI)
Primary efficacy endpoint			
Treatment failure (primary endpoint), n (%)†‡	9 (60)*	3 (19)	3.20 (1.06 to 9.62)
Components of failure			
Total patients receiving >1 IA glucocorticoid injection, n (%)‡	2 (13)	1 (6)	2.13 (0.22 to 21.17)
Total patients starting non-methotrexate conventional synthetic DMARD(s), n (%)‡	0 (0)	1 (6)	0 (NA)
Total patients starting biologic DMARD(s), n (%)‡	8 (53)	3 (19)	2.84 (0.92 to 8.76)
Key secondary efficacy endpoints			
Change from baseline in HAQ-DI score§¶	−0.07 (−0.22 to 0.09)*	−0.30 (−0.44 to −0.15)	0.23 (0.02 to 0.44)
ACR20 response, n (%)‡**	7 (47)	8 (50)	0.93 (0.45 to 1.94)
Change from baseline in SPARCC Enthesitis Index score††‡‡	−1.9 (−3.5 to −0.3)	−4.3 (−5.8 to −2.8)	2.3 (0.1 to 4.5)
Other secondary efficacy endpoints			
Modified PsARC response n (%)‡§§	11 (73)	13 (81)	0.90 (0.61 to 1.33)
Change from baseline in DLQI score¶,¶¶***	−1.5 (−3.5 to 0.5)	0.8 (−0.9 to 2.4)	−2.2 (−4.9 to 0.4)
Change from baseline in PASI score‡‡***†††	0.1 (−3.7 to 3.9)	0.3 (−2.4 to 2.9)	−0.2 (−4.8 to 4.5)
Change from baseline in the number of digits affected with dactylitis‡‡***	−1.2 (−2.1 to −0.2)	−1.5 (−2.7 to −0.4)	0.3 (−1.2 to 1.8)
ACR50 response, n (%)‡**	3 (20)	8 (50)	0.40 (0.13 to 1.23)
ACR70 response, n (%)‡**	1 (7)	6 (38)	0.18 (0.02 to 1.31)
Change from baseline in patient's global assessment, VAS¶‡‡‡	−4.3 (−14.8 to 6.3)	−25.6 (−35.4 to −15.7)	21.3 (6.9 to 35.7)
Change from baseline in arthritis pain, VAS¶‡‡‡	−8.8 (−19.1 to 1.6)	−24.8 (−34.6 to −15.0)	16.0 (1.8 to 30.3)
Change from baseline in fatigue, VAS¶‡‡‡	−0.0 (−11.5 to 11.5)	−18.1 (−29.0 to −7.2)	18.0 (2.2 to 33.9)
Change from baseline in tender joint count‡‡	−5.2 (−9.8 to −0.6)	−9.9 (−14.2 to −5.5)	4.72 (−1.6 to 11.0)
Change from baseline in C reactive protein§§§	0.4 (−1.0 to 1.7)	−1.0 (−2.3 to 0.2)	1.4 (−0.4 to 3.2)

All analyses were performed according to the intention-to-treat principle.

*P<0.05 for comparison with sham. Statistical testing was stopped following ACR20 in accordance with the predefined testing hierarchy.

†Treatment failure was defined as need for at least one of the following: more than one intra-articular glucocorticoid injection, and non-methotrexate conventional synthetic and/or biologic disease-modifying antirheumatic drugs.

‡Comparison was calculated as risk ratios based on crude relative risk.

§HAQ-DI score ranges from 0 to 3, with higher scores indicating greater disability.

¶Comparison was calculated as least squares means based on repeated measures linear mixed model across time points (baseline and weeks 1, 2, 3, 4, 12 and 26).

**ACR20/50/70 response (≥20%/50%/70% improvement from baseline in the number of tender and swollen joints and in at least 3 of 5 other specified domains).

††SPARCC Enthesitis Index score ranges from 0 to 16, with higher scores indicating more severe disease.

‡‡Comparison was calculated as least squares means based on repeated measures linear mixed model across time points (baseline and weeks 12 and 26).

§§Modified PsARC response (two of the following, one of which has to be a tender (68) and swollen (66) joint count, and no worsening of any measure: tender or swollen joint count improvement of 30% and/or patient global or physician global improvement of at least 1 point on the 5-point Likert scale).

¶¶DLQI score ranges from 0 to 30, with higher scores indicating more severe disease.

***PASI score, DLQI score and dactylitis count only in patients with baseline value >0.

†††PASI score ranges from 0 to 72, with higher scores indicating more severe disease.

‡‡‡VAS of 0–100, with higher scores indicating greater disease activity or pain.

§§§Comparison was calculated as least squares means based on repeated measures linear mixed model across time points (baseline and weeks 4, 12 and 26).

ACR, American College of Rheumatology; DLQI, Dermatology Life Quality Index; DMARD, disease-modifying antirheumatic drug; FMT, faecal microbiota transplantation; HAQ-DI, Health Assessment Questionnaire Disability Index; IA, intra-articular; NA, not available; PASI, Psoriasis Area Severity Index; PsARC, Psoriatic Arthritis Response Criteria; SPARCC, Spondyloarthritis Research Consortium of Canada; VAS, Visual Analogue Scale.

between two proportions (35% vs 70%) with a significance level of 5% (see further details in online supplemental appendices S1 and S2). In April 2019, we decided to stop recruitment by 31 December 2019, thereby adhering to the original planned trial completion date of 1 July 2020 (see online supplemental appendix S3). The main reason for this was that essential funding would stop following this date. Due to a slower than expected recruitment rate, only 31 participants were enrolled.

Patient involvement
Patients were directly involved in the design, funding, recruitment, conduct, reporting and dissemination of the study (see description at the end of the manuscript).

Statistical analysis
Analyses were based on the intention-to-treat (ITT) population including all randomised individuals, independent of subsequent adherence to the trial protocol. To assess the effect of FMT on the risk of treatment failure during the 26-week trial, we compared groups using risk ratios with 95% CIs based on an unadjusted (crude) model. Time-to-treatment failure was analysed based on a Kaplan-Meier plot from baseline to week 26 using Cox regression to estimate the HR with 95% CI and p value. Primary analyses in the ITT population at week 26 were based on a conservative treatment failure imputation default option for binary outcomes and a mixed-effects repeated measures model for continuous variables. For continuous outcome measures, we modelled between-group differences in outcomes at 0, 1, 2, 3, 4, 12 and 26 weeks with mixed-effects models, using time and group as categorical fixed-effect factors, interactions between time and group, random intercepts, and an unstructured covariance matrix; these models are reported as least squares means (and the difference between them) with 95% CIs.

All p values and 95% CIs were two-sided. We did not apply adjustments for multiplicity, rather we analysed the three key secondary outcomes in a prioritised order with a gatekeeping rule for serial testing. The other secondary outcomes are presented without conducting any formal statistical testing. Safety data are summarised descriptively in the full analysis set. In addition, we conducted a per-protocol analysis (see online supplemental table S1 and online supplemental figure S1) which included participants in whom the assigned transplant was successfully transferred into the third part of the duodenum. In addition, participants were excluded (censored) from the analysis following the day where they were categorised as treatment failures. Results of additional sensitivity analyses (including analyses based on the ITT population with missing data handled with multiple imputation) are presented in online supplemental table S2. We performed analyses using StataSE-64 V.16.1.

RESULTS

Participants

We enrolled participants to the trial between 16 May 2017 and 11 December 2019 at one Danish tertiary referral hospital (nationwide recruitment) with 26-week follow-up until 2 June 2020. Of 97 patients screened, 31 (32%) fulfilled the study requirements and were randomised to FMT or sham transplantation. All received the assigned intervention and 30 (97%) completed the clinical evaluation at week 26 (figure 1). Demographics and clinical characteristics of the two groups were comparable at baseline (table 2), except for some imbalance in sex and disease duration. Of the 31 participants, 27 (87%) had a personal history of skin psoriasis. A complete list of medication is presented in online supplemental table 4.

Safety

We observed no serious AEs or deaths in any of the groups. Forty-seven AEs occurred in 14 participants (93%) receiving FMT, and 53 AEs occurred in 14 participants (88%) receiving sham. No participants withdrew from the trial due to AEs. In the FMT group, AEs were mainly related to the gastrointestinal tract and included abdominal discomfort, flatulence, nausea and vomiting. One case of diverticulitis was deemed unrelated to FMT because the participant had a history of diverticulitis before trial enrolment and the episode occurred 24 weeks after FMT.

Three AEs were deemed related to the gastroscopic procedure. Of those, facial capillary rupture and uncontrolled defaecation both occurred within an hour of the procedure. The third procedure-related AE was exacerbation of known asthmatic disease (grade 2) 3 days after the procedure. This participant vomited during the gastroscopy. We did not suspect pulmonary aspiration, and the clinical evaluation (including measures of C reactive protein) performed by the participant's general practitioner 4 and 7 days after the procedure did not suggest an underlying bacterial aetiology. A complete list of AEs, routine laboratory findings and metabolic changes is presented in table 3.

Efficacy

During the entire 26 weeks of observation, the rate of the primary outcome (treatment failure) was significantly higher in the FMT than in the sham group (HR, 4.87 (95% CI 1.31 to 18.18); p=0.018) (see figure 2). After 26 weeks, treatment had failed in more FMT-treated participants (9 of 15, 60%) than sham-treated participants (3 of 16, 19%) (crude relative risk, 3.20 (95% CI 1.06 to 9.62); p=0.018) (see table 1).
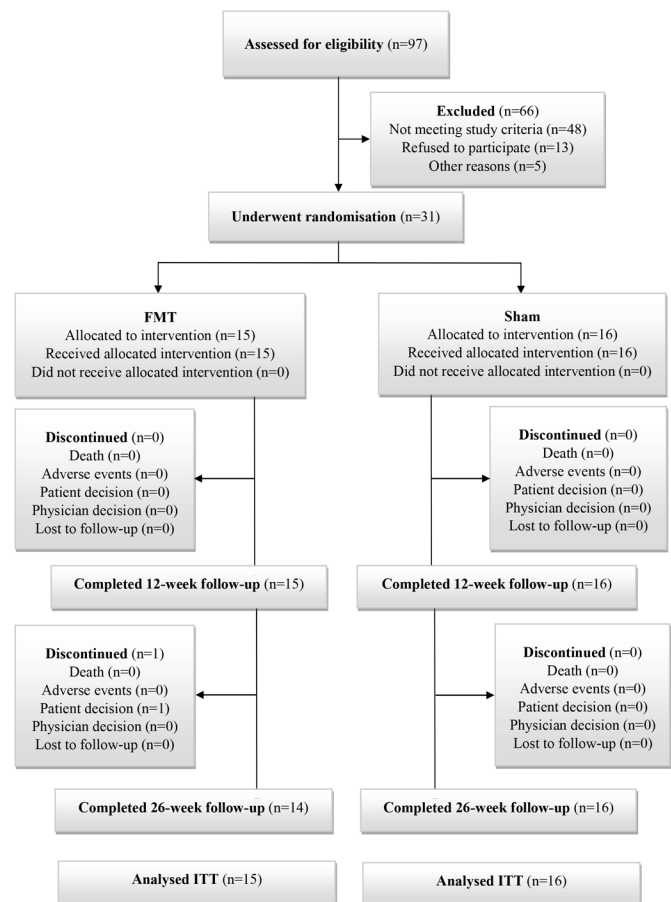

Figure 1 Patient disposition. Reasons for not meeting study criteria (n=48): not diagnosed with psoriatic arthritis (n=5), not ≥3 swollen joints (n=11), treated with other csDMARD (n=2) or bDMARD (n=5), methotrexate (≥15 mg/week) toxicity (n=6), age below or above limit (n=3), systemic inflammatory comorbidity (n=1), living abroad (n=14) and closed inclusion 2 days after initial contact (n=1). bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FMT, faecal microbiota transplantation; ITT, intention-to-treat.

Starting biologic disease-modifying antirheumatic drug was the main reason for being categorised as treatment failure (8 of 15 (53%) vs 3 of 16 (19%)). In the FMT group, eight patients (53%) had initiated biologic therapy at the 12-week visit compared with two (13%) in the sham group. The median time from trial intervention to starting biologics was 32 days (IQR 23–64) in the FMT group and 99 days (IQR 60–175) in the sham group. The median time from starting biologics to evaluation at week 26 was 155 days (IQR 118–173; total group exposure time, 995 days) in the FMT group and 70 days (IQR 0–126; total group exposure time, 196 days) in the sham group.

The HAQ-DI decreased more (indicating better physical function) in the sham group than in the FMT group (least squares means, −0.30 (95% CI −0.44 to −0.15) vs −0.07 (95% CI −0.22 to 0.09), difference 0.23 (0.02 to 0.44); p=0.031). The trajectories for HAQ-DI by treatment group from baseline to week 26 are presented in figure 3. Hierarchical statistical testing failed with regard to the proportion of ACR20 responders when comparing the FMT group with sham (7 of 15 (47%) vs 8 of 16 (50%); crude relative risk, 0.93 (0.45 to 1.94)).

Table 2 Baseline demographics and disease characteristics

Characteristics	FMT (n=15)	Sham (n=16)	Total (N=31)
Female sex, n (%)	8 (53)	12 (75)	20 (65)
Age, years	48.9 (16.1)	52.4 (11.0)	50.7 (13.6)
Height, cm	175.2 (7.0)	169.8 (8.6)	172.4 (8.2)
Weight, kg	93.6 (15.4)	92.4 (24.8)	93.0 (20.5)
Time since diagnosis, years*	2.6 (0.3–5.8)	5.6 (0.5–8.8)	3.7 (0.5–8.3)
Rheumatoid factor IgM negative, n (%)†	13 (93)	15 (94)	28 (93)
Anticitrullinated peptide antibody negative, n (%)†	14 (100)	16 (100)	30 (100)
HLA-B27 negative, n (%)	15 (100)	13 (81)	28 (90)
C reactive protein, mg/L	4.98 (7.18)	5.54 (5.87)	5.27 (6.43)
HAQ-DI‡	0.89 (0.51)	0.78 (0.50)	0.83 (0.50)
Swollen joint 66 count	7.5 (3.0)	6.7 (2.7)	7.1 (2.8)
Tender joint 68 count	14.9 (8.9)	17.3 (8.8)	16.1 (8.8)
SPARCC Enthesitis Index§			
Score ≥1, n (%)	13 (87)	15 (94)	28 (90)
Score in patients with a score ≥1	8.1 (4.3)	7.2 (3.3)	7.6 (3.8)
Dactylitis			
Affected digit(s) ≥1, n (%)	6 (40)	4 (25)	10 (32)
Digits affected in patients with affected digit(s) ≥1	1.5 (0.5)	1.5 (0.6)	1.5 (0.5)
Physician's global assessment of disease activity, VAS¶	35.1 (15.8)	31.4 (13.0)	33.2 (14.3)
Patient's global assessment of disease activity, VAS¶	56.1 (22.3)	56.0 (23.7)	56.0 (22.7)
Arthritis pain, VAS¶	54.1 (23.3)	48.8 (19.9)	51.9 (21.3)
Fatigue, VAS¶	56.5 (26.2)	57.4 (26.4)	57.0 (25.9)
Presence of nail disease, n (%)	12 (80)	10 (63)	22 (71)
PASI**			
Score >0, n (%)	4 (27)	6 (38)	10 (32)
Score in patients with a score of more than 0	1.07 (2.09)	1.39 (2.17)	1.24 (2.11)
DLQI score††			
Score >0, n (%)	9 (60)	12 (75)	21 (68)
Score in patients with a score of more than 0	2.1 (3.9)	1.8 (1.7)	1.9 (2.9)
Methotrexate			
Oral administration route, n (%)	2 (13)	4 (25)	6 (19)
Oral dose, mg/week	15.0 (0.0)	20.0 (4.1)	18.3 (4.1)
Subcutaneous administration route, n (%)	13 (87)	12 (75)	25 (81)
Subcutaneous dose, mg/week	20.0 (4.1)	20.0 (3.7)	20.0 (3.8)
Previous use of biologic DMARD, n (%)	2 (13)	3 (19)	5 (16)
Previous use of non-methotrexate conventional synthetic DMARD, n (%)	4 (27)	3 (19)	7 (23)
Antibiotics within 1 year of inclusion, n (%)	4 (27)	6 (38)	10 (32)
Positive IgG serology‡‡			
Yersinia, n (%)	0 (0)	1 (6)	1 (3)
Campylobacter, n (%)	0 (0)	0 (0)	0 (0)
Salmonella, n (%)	0 (0)	1 (6)	1 (3)
Faecal calprotectin, mg/kg§§	29 (17–63)	27 (15–72)	28 (15–68)
Stool frequency per week	10.4 (3.7)	10.7 (4.3)	10.6 (4.0)
Bristol Stool Scale score¶¶	4.3 (1.3)	3.6 (1.3)	4.0 (1.3)
Presence of gastrointestinal symptoms within the last week			
Abdominal pain¶	14.1 (14.7)	23.9 (23.4)	19.2 (20.0)
Pyrosis, n (%)	2 (13)	2 (13)	4 (13)
Nausea, n (%)	6 (40)	3 (19)	9 (29)
Vomiting, n (%)	1 (7)	0 (0)	1 (3)
Mucus in the stool, n (%)	3 (20)	1 (6)	4 (13)
Blood in the stool, n (%)	1 (7)	0 (0)	1 (3)
Smoking status			
Current, n (%)	5 (33)	4 (25)	9 (29)

Table 2 Continued

Characteristics	FMT (n=15)	Sham (n=16)	Total (N=31)
Previous, n (%)	4 (27)	8 (50)	12 (39)
Never, n (%)	6 (40)	4 (25)	10 (32)
Alcohol consumption, units per week	0.9 (0.9)	0.8 (0.6)	0.8 (0.7)

Data are mean (SD) or n (%) unless otherwise stated.

*Time since diagnosis of psoriatic arthritis is presented as median and IQR.

†Presence of rheumatoid factor (IgM) and anticitrullinated peptide antibody was not accessed in one patient from the FMT group.

‡HAQ-DI scores range from 0 to 3, with higher scores indicating greater disability.

§SPARCC Enthesitis Index scores range from 0 to 16, with higher scores indicating more severe disease.

¶This evaluation is based on a VAS of 0–100, with higher scores indicating greater disease activity or pain.

**PASI scores range from 0 to 72, with higher scores indicating more severe disease.

††DLQI scores range from 0 to 30, with higher scores indicating more severe disease.

‡‡Serology specification: *Salmonella enteritidis* and *S. typhimurium*, *Yersinia enterocolitica*, and *Campylobacter coli* and *C. jejuni*.

§§Median (IQR). Lower detectable limit of faecal calprotectin is 15 mg/g.

¶¶Bristol Stool Scale scores range from 1 to 7, with types 1 and 2 indicating constipation, types 3 and 4 normal, and types 5–7 tending towards diarrhoea (loose to watery stool).

DLQI, Dermatology Life Quality Index; DMARD, disease-modifying antirheumatic drug; FMT, faecal microbiota transplantation; HAQ-DI, Health Assessment Questionnaire Disability Index; HLA-B27, human leukocyte antigen-B27; PASI, Psoriasis Area Severity Index; SPARCC, Spondyloarthritis Research Consortium of Canada; VAS, Visual Analogue Scale.

DISCUSSION

Modification of the immunogenic, intestinal microbial communities and their metabolites associated with immune-mediated diseases has been highlighted as a possible way to either directly or indirectly modulate a dysregulated immune response in the recipient. In this first FMT trial in PsA, we performed one upper, single-donor FMT to evaluate safety and efficacy in patients with active, peripheral PsA treated with steady state dose methotrexate (≥15 mg/week). Most importantly, one FMT appeared to be safe in this patient population. Contrary to our hypothesis, the rate of treatment failure (ie, patients needing treatment intensification) was significantly higher in the FMT group than in the sham group. Likewise, the HAQ-DI improved more in sham-treated (indicating better physical function) than in FMT-treated patients.[26] The event curve (figure 2) demonstrates that treatment failure occurred very quickly after the procedure in patients receiving FMT. Because of the comparable disease activity between groups at baseline, our findings suggest that FMT from selected donors can worsen the symptoms of PsA. This contrasts a case report of a patient with PsA where FMT seemed to assert beneficial effects on the arthritic disease.[27]

FMT for other immune-mediated conditions such as IBD has demonstrated local therapeutic immune-modulating abilities, and disease flares following FMT seem to occur in similar rates among control group patients.[13] Although transient increase in C reactive protein and self-limiting fever are well-known side effects associated with an immunological response in patients receiving FMT for *C. difficile* infection and/or IBD,[28] based on the existing evidence, thoroughly screened stool for FMT is in general considered safe and has not been related to severe immune responses. Hence, our findings add to the growing body of evidence suggesting a gut–joint axis in the pathogenesis of PsA.[29 30]

A strength of our study is that we designed the trial to provide results relevant to clinical practice. This included the use of FMT products from routine treatment of recurrent *C. difficile* infections, the timing of the intervention, the long follow-up, the allowance of antibiotics and other medication during follow-up (except for non-methotrexate disease-modifying antirheumatic drugs), and the lack of diet restrictions. Due to the randomised design, allocation concealment, masking of patients and treating rheumatologists/outcome assessors, high treatment adherence, low attrition, no missing data on the primary outcome, and only few cases of protocol violations (see online supplemental text S1), we deem the risk of bias to be low. Furthermore, because our decision to stop the trial before reaching 80 patients was made independently of the trial findings, we do not expect that this decision has biased the results.[31] Nevertheless, the small study population did affect the precision of the trial estimates, making the conclusions less robust.

Limitations include the initiation of additional disease-modifying antirheumatic drugs in patients experiencing treatment failure, which may likely have exerted positive effects on the secondary outcomes (HAQ-DI, ACR20 and SPARCC Enthesitis Index) evaluated at week 26. Although this may especially be true for the FMT group, where the majority of participants received biologics within the first 12 weeks of the trial, this explanation is not valid in the sham group, where less than one in five received additional treatment. Hence, the significant clinical improvement observed in this group suggests the presence of trial participation effects.[32] Findings from a qualitative study nested within the trial support this notion.[33] Nevertheless, based on the double-blind, randomised design and the fairly comparable demographics and disease characteristics of FMT-treated and sham-treated patients at baseline, we have no reason to believe that exposure, intensity and susceptibility of these effects differed between groups.[34]

The compositional nature of the primary endpoint combining both the patient's values, preferences and needs in relation to the outcome domains that were important to him/her (eg, pain, physical function, fatigue and social participation) with the physician's assessment of disease (eg, musculoskeletal disease activity and systemic inflammation), in addition to the very high ACR50/70 response in the sham group, complicated the interpretation of the trial results. For example, we cannot rule out that parts of patients' perceptions of the disease, and the resulting motivation for receiving additional treatment, could have been affected by elements of the disease not related to active inflammation (which was our hypothesised target of the FMT) such as central sensitisation and structural damage. In addition, while measures of disease activity appeared comparable between groups at baseline, the (random) imbalance in sex and disease duration could hypothetically have had an effect on the between-group differences in the primary and secondary outcomes.

Table 3 Adverse events through 26 weeks

AE events*	FMT (n=15) PYRS=7.4	Sham (n=16) PYRS=8.5
Total AEs, n	57	53
Total patients with AE, n (%)	14 (93)	14 (88)
Total SAEs, n	0	0
Total patients with SAE, n (%)	0	0
Withdrawal due to any AE, n (%)	0	0
Withdrawal due to any SAE, n (%)	0	0
Death, n (%)	0	0
AEs of special interest†		
Change from baseline in abdominal pain, VAS‡§	8.8 (1.9 to 15.7)	−18.0 (−24.5 to −11.4)
Change from baseline in Bristol Stool Scale score, types 1–7§¶	−0.2 (−0.7 to 0.3)	0.0 (−0.5 to 0.5)
Change from baseline in faecal calprotectin, mg/kg**	86 (−60 to 324)	16 (−36 to 69)
Total episodes of patient-reported fever, n	13	12
Patients treated with antibiotics, n (%)	2 (13)	5 (31)
Nausea, n (%)	9 (60)	7 (44)
Reflux, n (%)	8 (53)	8 (50)
Vomiting, n (%)	6 (40)	1 (6)
Blood in the stool, n (%)	0 (0)	1 (6)
Mucus in the stool, n (%)	4 (27)	0 (0)
Elevated plasma alanine aminotransferase (men >70 U/L; women >45 U/L), n (%)	2 (13)	5 (31)
Abnormal white cell count		
Low (<3.50×10⁹/L), n (%)	0 (0)	0 (0)
High (>8.80×10⁹/L), n (%)	5 (33)	6 (38)
Abnormal platelet count		
Low (men <145×10⁹/L; women <165×10⁹/L), n (%)	0 (0)	1 (6)
High (men >350×10⁹/L; women >400×10⁹/L), n (%)	1 (7)	2 (13)
Low level of haemoglobin (men < 134 g/L; women < 118 g/L), n (%)	3 (20)	1 (6)
Change in weight, kg††	0.9 (−0.6 to 2.3)	−0.1 (−1.5 to 1.2)
Change in haemoglobin A1c level, mmol/mol††	1.43 (0.35 to 2.52)	0.31 (−0.70 to 1.33)
Change in plasma cholesterol level, mmol/L††	0.23 (−0.03 to 0.49)	−0.08 (−0.31 to 0.16)
Change in plasma low-density lipoprotein cholesterol level, mmol/L††	0.13 (−0.08 to 0.34)	−0.14 (−0.33 to 0.05)
Change in plasma high-density lipoprotein cholesterol level, mmol/L††	0.05 (−0.05 to 0.15)	−0.01 (−0.10 to 0.08)
Change in plasma triglyceride level, mmol/L††	−0.01 (−0.37 to 0.34)	0.15 (−0.17 to 0.47)
Other reported AEs, n (%)†		
Pneumonia	1 (7)	1 (6)
Gastroenteritis	0 (0)	1 (6)
Sinusitis	0 (0)	1 (6)

Continued

Table 3 Continued

AE events*	FMT (n=15) PYRS=7.4	Sham (n=16) PYRS=8.5
Wound infection	0 (0)	1 (6)
Cystitis	1 (7)	1 (6)
Conjunctivitis	0 (0)	1 (6)
Diverticulitis	1 (7)	0 (0)
Influenza symptoms	0 (0)	1 (6)
Bronchial asthma exacerbation	1 (7)	0 (0)
Benign paroxysmal positional vertigo	0 (0)	1 (6)
Flatulence	1 (7)	0 (0)
Uncontrolled defaecation	1 (7)	0 (0)
Facial capillary rupture	0 (0)	1 (6)

Full analysis set: all patients who were randomly assigned to a study group and had exposure to the intervention (FMT or sham) independent of group.

*Any AEs: data are number of events or number of patients (%). Treatment with antibiotics was not counted as a separate AE.

†AEs of special interest and other reported AEs: dichotomous data are number of patients with at least one episode (%) unless otherwise specified.

‡VAS of 0–100, with higher scores indicating greater disease activity or pain.

§Abdominal pain and Bristol Stool Scale score are reported as the main effect of group based on a repeated measures linear mixed model across time points (baseline, week 1, week 2, week 3, week 4, week 12 and week 26).

¶Bristol Stool Scale score ranges from 1 to 7, with types 1 and 2 indicating constipation, types 3 and 4 normal, and types 5–7 tending towards diarrhoea (loose to watery stool).

**Faecal calprotectin is reported as the main effect of group based on a repeated measures linear mixed model (bootstrap SE) across time points (baseline, week 4, week 12 and week 26).

††The metabolic markers (weight, haemoglobin A1c, cholesterol and triglyceride) are evaluated as change from baseline to week 26. Positive values signify an increase, whereas negative values signify a decrease.

AE, adverse event; FMT, faecal microbiota transplantation; PYRS, person years at risk; SAE, serious adverse event; VAS, Visual Analogue Scale.

Furthermore, the participants of our trial constituted primarily adults with active, polyarticular PsA, which is a relatively rare condition in clinical practice.[20] Consequently, although the spectrum of patients with PsA that are enrolled in pharmacological trials is skewed towards this study population, the ability to generalise our findings to the majority of patients with PsA is limited. Moreover, because only 10 participants (32%) had active skin psoriasis at the time of inclusion, this trial was not suited for assessment of the potential of microbiota modulation in cutaneous inflammation. Finally, our study was neither large enough nor long enough to evaluate uncommon serious AEs and long-term risks.[35]

Previous findings in patients with ulcerative colitis indicate that one FMT regimen performed within 1 week is insufficient to maintain long-lasting (12 months) local anti-inflammatory response in the majority of patients with a beneficial response after 8 weeks.[36] Hence, we could have missed early clinical significant changes in the secondary outcomes that abated before the 26-week evaluation. In addition, pooled donor batches and high-intensity induction of FMT followed by frequent administration of donor transplant seem to enhance the chances for clinical remission in ulcerative colitis.[36–38] Perhaps as importantly, previous successes of FMT in IBD appear to have been driven by 'super-donors' characterised by the presence or absence of specific bacteria species.[36 39] To further complicate this picture, matching of donor and recipient could be another important factor to consider.
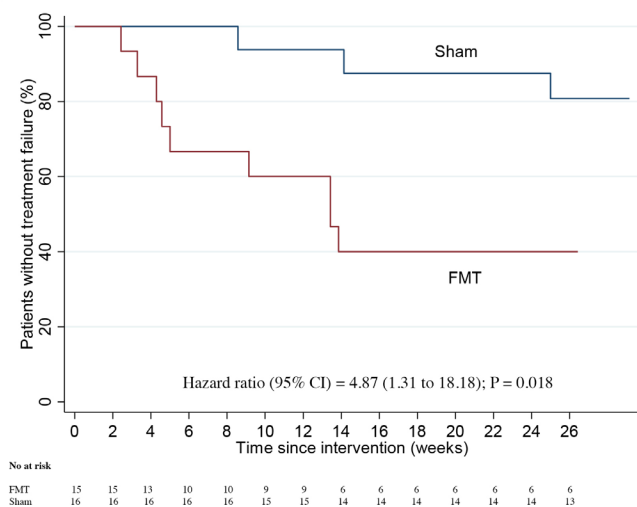
Figure 2 Event curves of treatment failure by intervention group from baseline to week 26. Time-to-treatment failure was analysed using survival analysis as Kaplan-Meier curves from baseline to week 26. Cox regression was used to provide an estimate of the HR with 95% CI and p value. The number of participants remaining at risk is displayed below the horizontal axis. Treatment failure was defined as need for at least one of the following: more than one intra-articular glucocorticoid injection, and non-methotrexate conventional synthetic and/or biologic disease-modifying antirheumatic drugs. FMT, faecal microbiota transplantation.

In conclusion, further investigation is needed to explore whether extrinsic factors related to the FMT method, such as single versus multiple donor batches, fresh versus frozen products, aerobic versus anaerobic environment, type of stool preparation protocol, storage time, freeze–thaw cycles, pretreatment preparation such as bowel lavage and antibiotics, delivery form, and overall treatment strategy (dose and frequency), may influence the outcome of FMT in PsA.[40] Future FMT trials could pursue an approach that is similar to the ones used in IBD studies.[41] Moreover, evaluation of dysbiosis in patients (or donors) prior to trial entry could hypothetically
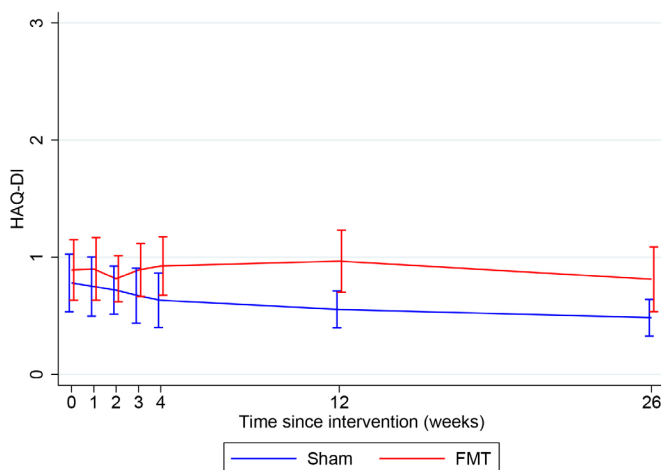
enhance FMT efficiency. Other mechanisms that should be thoroughly investigated in future studies include the degree and durability of donor microbiota engraftment, changes in patients' microbiota following FMT and comparator intervention, and characterisation of 'good' and 'bad' donations. Indeed, the lack of comprehensive microbiota analyses is a limitation of the current study.

In this preliminary randomised controlled trial with focus on safety, we did not observe any serious AEs. Although no firm conclusions can be drawn from this small trial and despite the similar proportions of ACR20 responders between groups at 26 weeks, our findings indicate that FMT may lead to worsening of PsA, suggesting a role of the intestinal microbiota in downstream immune effects of this disease. Larger, randomised trials of FMT where a sufficient amount of participants will be included combined with exploration of immunological effects and indepth analyses of the composition and functional potential of the microbiota in donor and recipients should be undertaken to further investigate the safety and potential benefits of therapeutic targeting of the gut–joint axis in immune-mediated arthritis.

Patient and public involvement

Patients and the public played an important part in all elements of the research process beyond the conception of the trial. In the design phase, we asked patients who attended the outpatient clinic to provide input on ethical challenges and trial logistics, especially regarding donor selection and method of FMT administration. Patients also gave feedback to the wording and design of patient information material and recruitment flyers. During the undertaking of the trial, we asked patient organisation and the public to assist the refinement of our recruitment strategy and to help with publicity and funding. Following the last trial visit and before unmasking, we interviewed 10 participants about their trial experiences, which provided insight into their motivation for participation, impact on everyday life, FMT acceptability, and factors related to the trial that may have promoted trial participation effects (the results of this qualitative study will be presented elsewhere). In the dissemination phase of the trial, we invited a patient research partner (MW), who did not participate in the trial, to become coauthor. He made valuable suggestions for improving the reporting of the study and helped us clarify the main findings as seen from a patient's perspective. Finally, we disseminated the results of the trial in a letter to all study participants and invited them to attend an online meeting, where we further explained and discussed the findings of the trial.

Figure 3 HAQ-DI scores by treatment group from baseline to week 26. Least squares means calculated from the repeated measures linear mixed model: intention-to-treat population. Bars indicate 95% CI. HAQ-DI scores range from 0 to 3, with higher scores indicating greater disability. FMT, faecal microbiota transplantation; HAQ-DI, Health Assessment Questionnaire Disability Index.

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