Faecal microbiota transplantation for *Clostridium difficile* infection resulting in a decrease in psoriatic arthritis disease activity

Sirs,

We describe a case of a woman with psoriatic arthritis, who after receiving faecal microbiota transplantation (FMT) for *Clostridium difficile* infection was able to cease her disease-modifying anti-rheumatic drugs (DMARDs) with sustained remission of her rheumatic symptoms. Therapeutic alteration of the gut microbiome with FMT has been demonstrated to be an effective therapy for Clostridium difficile infection and ulcerative colitis, with trials underway in many other diseases (1). Changes in the composition of the gut microbiome, termed dysbiosis, have already been implicated in gut diseases such as *Clostridium difficile* infection (2). There are emerging data to support to role of dysbiosis in the pathogenesis of rheumatic disease (3), thereby raising the possibility of therapeutic alteration of the gut microbiome having an impact on disease activity in psoriatic arthritis.

A 59-year-old woman with a history of psoriatic arthritis presented to our institution in July 2016 with diarrhoea of up to twenty motions per day having recently completed a course of oral clindamycin for presumed facial cellulitis. The patient had been diagnosed with psoriatic arthritis in 2004 with recurrently active spondyloarthropathy and polyarthritis, manifested as sacroiliac joint pain and stiffness, and synovitis of the small joints of the feet, left ankle and right knee. Previous whole body bone scan had demonstrated sacroiliitis, although plain x-ray did not demonstrate erosions and an MRI was never performed. Mild psoriasis was her only extra-articular manifestation and had not been present for many years. In the 3 months preceding presentation, she complained of increased duration of morning stiffness to between 2-3 hours and increased pain in multiple joints including the sacroiliac joints. Clinically she had a left ankle effusion, a small-moderate right knee effusion, synovitis in left second to fourth metatarsal phalangeal joints and left sided plantar fasciitis. Tender and swollen joint count (TSJC) was 8. C-reactive protein (CRP) rose from baseline 1.3mg/L to 17mg/L and ESR from baseline 5mm/hour to 15mm/hour. Her regular medications at the time of presentation were 25mg per week methotrexate (oral), hydroxychloroquine 200mg twice a day, leflunomide 10mg daily, folic acid and paracetamol. She had previously trialed salazopyrin (allergic rash) and leflunomide 20mg daily (gastrointestinal intolerance). On examination her heart rate was 72 beats per minute, blood pressure 113/53 mmHg, temperature 36.6 degrees Celsius and her abdomen was soft and non-tender on palpation. Her peripheral blood white cell count was 18.5 x 10^9/L, CRP 84mg/L and the polymerase chain reaction testing of her stool yielded a positive result for *Clostridium difficile* toxin B DNA. Her methotrexate, leflunomide and hydroxychloroquine were held. A flexible sigmoidoscopy revealed diffuse moderate inflammation in the sigmoid colon with pseudomembranous plaques (Fig. 1).

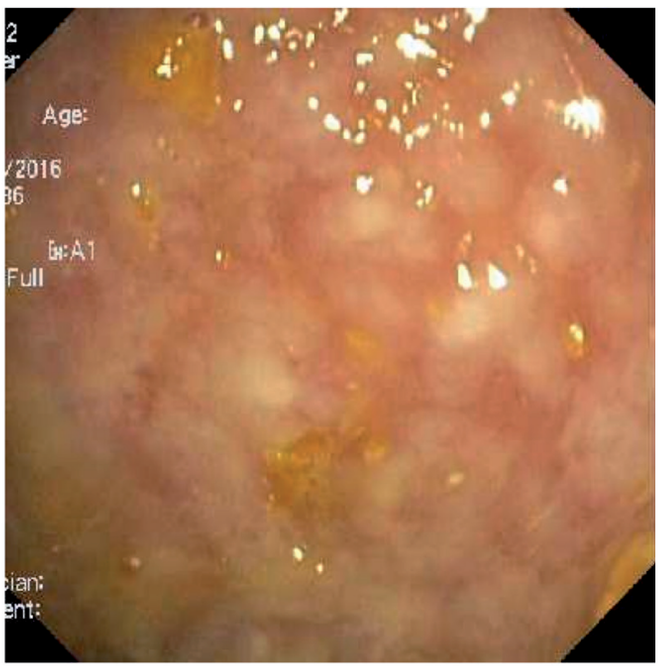

Fig. 1. Colitis with pseudo-membranes seen on flexible sigmoido-scopy.

Biopsies showed acute active mucosal inflammation with no evidence of chronicity. A diagnosis of *Clostridium difficile* colitis was made, and she was commenced on intravenous metronidazole, followed by intravenous vancomycin. Despite six days of therapy she had persistent diarrhoea in excess of ten stools a day, with associated fevers to 38.1 degrees Celsius and a rise in her CRP to 140 mg/L. The decision was made to administer FMT via colonoscopy. At three days post-FMT she had improved with a reduction of stool frequency to once a day, had no further fevers and normalisation of her CRP.

The patient reported dramatic improvement in her joint symptoms in the weeks following FMT and on review at one month, four months and ten months following the FMT she achieved recognised minimal disease activity state for her psoriatic arthritis (4, 5) with minimal morning stiffness, no sacroiliac joint pain, a TSJC of zero and normal inflammatory markers, whilst remaining off all DMARDs. At review thirteen months following FMT, the patient reported increase in disease activity with diffuse arthritis and increase in morning stiffness, a TSJC of 10 and CRP of 6.3mg/L. The return of symptoms coincided with an episode of traveller's diarrhoea. The patient was reluctant to restart immunosuppression due to a fear of infection, so a compromise of oral methotrexate at 10mg/week was commenced with partial response. With regards to extra-articular disease, the patient had not had active psoriasis for over 24 months before the FMT, and there was no recurrence after the FMT, so we cannot comment on the effect of FMT on psoriatic skin disease in this patient.

To our knowledge, this is the first case report of FMT being associated with attainment of minimal disease activity in psoriatic arthritis.

Studies using 16s RNA sequencing have found significant differences in the both the gut and cutaneous microbiota of psoriasis patients compared to controls (6). Patients with psoriatic arthritis have been noted to have low levels of Akkermansia mucinophilia species and Ruminococcus genera compared to controls (6). These are bacteria that have anti-inflammatory properties and are known to contribute to gut homeostasis (7).

The gut microbiota can influence local and systemic immune responses via alterations in intestinal permeability, molecular mimicry and activation of effector immune cells (8). Psoriatic arthritis is known to be a T cell-mediated disease, in which pathogenic T cells produce IL-17 in response to IL-23. This is supported by the fact that IL-17 producing T cells (Th17) are found in affected tissues (9) as well by the fact that agents that target the IL-23/Th17 pathway (*e.g.* ustekinumab) appear to be efficacious. In a mouse model, segmented filamentous bacteria induced autoimmune arthritis through the ability to specifically promote differentiation of the Th17 subset (10). It is therefore plausible that gut dysbiosis may directly contribute to the direction of dif-

ferentiation of naïve T cells into specific effector T cells that drive the pathogenesis of psoriatic arthritis.

The outcome in this case is hypothesis-generating in that it suggests that the gut microbiome may play an aetiological role in psoriatic arthritis and there may be the potential to treat psoriatic arthritis with gut microbial manipulation. Clinical trials aimed at modulating the gut microbiome using FMT or defined microbial consortia are required to further investigate these possibilities.

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Competing interests: none declared.

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