

Clinical and immunologic effects of faecal microbiota transplantation in a patient with collagenous colitis

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Abstract

One to six percent of patients with microscopic colitis are refractory to medical treatment. The effect of faecal microbiota transplantation (FMT) in active collagenous colitis (CC) has, to the best of our knowledge, never been reported before. Here, we report the effect of repeated FMT in a patient with CC. The patient presented with severe symptoms including profuse diarrhea and profound weight loss. Although she responded to budesonide in the beginning, she became gradually refractory to medical treatment, and was therefore treated with FMT. The patient remained in remission for 11 mo after the third faecal transplantation. The immunomodulatory effect of the therapy was evaluated using flow cytometry, which showed alterations in the profile of intraepithelial and lamina propria lymphocyte subsets after the second transplantation. Our observations indicate that FMT can have an effect in CC, which support the hypothesis that luminal factors, influencing the intestinal microbiota, are involved in the pathogenesis of CC.

Key words: Faecal microbiota transplantation; Microbiota;

Collagenous colitis; Flow cytometry; Lymphocytes

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Core tip: Collagenous colitis (CC) is characterized by chronic watery diarrhea and inflammation in the colonic mucosa. The treatment is based on budesonide or immunomodulatory treatment in moderate to severe cases. However, some patients do not respond to the treatment. The aim of this article is to report the effect of repeated faecal microbiota transplantation in a CC patient who remained in remission 11 mo after the repeated transplantations, which also caused alterations in the lymphocyte subsets.

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INTRODUCTION

Microscopic colitis (MC) is a chronic inflammatory disease of the colon, characterized clinically by chronic watery diarrhea, abdominal pain and weight loss^[1]. Based on histopathological features in the colon mucosa, MC comprises primarily two entities; collagenous colitis (CC) and lymphocytic colitis (LC). Both CC and LC are characterized by inflammation in the lamina propria of the colon mucosa. CC, however, is distinguished from LC by a colonic subepithelial collagen band of 10 µm or more in thickness, whereas LC has a more pronounced lymphocyte infiltration in the colonic epithelium^[2]. The pathogenesis of MC is not known, but it is thought to be multifactorial, involving a mucosal immune response to luminal factors in genetically predisposed individuals. Defects in the epithelial barrier function may lead to transmucosal passage of antigens and bacteria, and consequently leading to inflammation as seen in MC^[3-5]. A role for the colonic microbiota or an invasive microorganism in the disease pathogenesis is supported by the observation that some CC patients clinically improve after treatment with antibiotics of different categories for concurrent infections^[6].

The treatment of MC was earlier based on retrospective studies: loperamide, cholestyramine, sulphasalazine and 5-aminosalicylic acid were the standard alternatives^[6]. During the last decades, it has become evident that budesonide is a very efficient drug and the drug of choice for MC with a moderate to severe course, alternatively azathioprine in steroid refractory cases^[7,8]. However, one to six percent of MC patients are refractory to conventional

medical treatment^[9], and surgery with an ileostomy has hitherto been the only option in severe medically refractory cases^[10].

Faecal microbiota transplantation (FMT) is a method to modify microbiota dysbiosis, and studies have shown that it can have effect in patients with ulcerative colitis, resulting in maintained clinical as well as endoscopic and histopathologic remission^[11-14]. For recurrent *Clostridium difficile* infection, FMT has for some decades, been established as an effective treatment^[15-18]. Despite microbiota showing dysbiosis in CC patients^[19,20], FMT as a possible treatment for CC has not been reported before. We here present a case with medically refractory CC, who responded to FMT.

CASE REPORT

Patient and donor characteristics, procedures and clinical results of FMT

The patient was a 72 year old female who suffered from frequent watery diarrhea and was diagnosed with CC six months after debut of symptoms in 2008. The diagnosis was based on clinical findings and histopathological evaluation which showed an increased number of lymphocytes in the lamina propria, in the epithelium and in a few crypts. There was a thickened collagenous band subepithelially. The findings were diffusely distributed in the whole colon^[2,7]. She had normal biochemical and hematologic parameters, whereas faecal calprotectin levels were increased from 160 mg/kg in 2009 to 500 mg/kg when the CC deteriorated in 2013. Stool cultures were tested for *Clostridium difficile* at diagnosis, before the first and before the second FMT, and were also negative for *Salmonella species*, *Shigella dysenteriae*, *Campylobacter jejuni*, and *Yersinia enterocolitica*. Based on histopathologic examination of duodenal biopsies, celiac disease was excluded. Initial treatment with loperamide had only little effect, and cholestyramine, had no effect. The patient responded well to budesonide, and was in remission for 2 years. Gradually, however, the effect of budesonide declined during 2013, and her symptoms worsened with profuse watery diarrhea, severe fecal incontinence, fatigue, and a weight loss of totally 15 kg, though, without biochemical signs of malabsorption. She tried mesalazine without effect, and azathioprine, but did not tolerate it. She had doxycycline in November 2013, 100 mg per day for 10 d as treatment for olecranon bursitis, which resulted in decreased numbers of daily stools, but the effect only lasted one week after the cessation of the antibiotic. She had one additional doxycycline cure in 2014, also with good but temporary antidiarrheal effect. The details for treatments are summarized in Table 1. The patient then learned about the possible effect of FMT in ulcerative colitis, and was interested in trying this treatment. As FMT has not been documented in CC, she was offered this

Table 1 Summary of the treatment and results in a collagenous colitis patient

Treatment	Result of the treatment
Loperamide 2-4 mg per day	Little effect
Cholestyramine, 4 g, three times per day	No effect
Mesalazine 800 mg twice per day for 4 mo	No effect
Budesonide capsules 3 mg 1-3 times per day	Good but declining effect after 2 yr of treatment
Azathioprine	Side effects (liver toxicity)
Doxycycline, 100 mg per day for 10 d, given twice	Good but temporary effect
First FMT, November 2014	General improvement for 2 wk
200 mL filtrate infused as an enema in the rectum for five consecutive mornings	Not fulfilling the criteria for remission ^[21]
Second FMT, March 2015	General improvement for 4 wk
300 mL filtrate instilled in cecum	Not fulfilling the criteria for remission
Third FMT, May 2015	Remission with normalized stools
300 mL filtrate instilled in cecum	and normal BMI achieved for 11 mo

Histopathologic findings before the first transplant and after the second transplant showed typical and similar features of CC. CC: Collagenous colitis; BMI: Body mass index; FMT: Faecal microbiota transplantation.

treatment after thorough information about possible side effects. The patient was informed of the study protocol before treatment and colonoscopy, and gave her written consent to donate tissue samples for research purposes and undergo treatment with FMT.

The patient's husband was selected as the donor of faecal microbiota. His feces were screened and found negative for *Salmonella species*, *Shigella dysenteriae*, *Campylobacter jejuni*, *Yersinia enterocolitica* and *Clostridium difficile* by culture. Furthermore, tests for haematology and liver enzymes were negative, as well as blood tests for hepatitis A, B and C and varicella zoster virus. The presence of serum antibodies against Epstein-Barr virus and cytomegalovirus indicated earlier, but no ongoing, infections.

The faecal sample from the donor was obtained 2-3 h before transplantation. Two tablespoons of feces were diluted and mixed in 500 mL 0.9% NaCl. The homogenized solution was filtered twice through a pre-sterilized metal sieve. At the first instillation procedure, 200 mL of the filtrate was infused over 1 h as an enema into the rectum of the patient, for five consecutive mornings according to our standard procedure for *C. difficile* treatment. Since the first FMT did not improve the clinical status of the patient, at the second and third instillation procedures, 300 mL filtrate was infused *via* a colonoscope into the cecum over 10 min (Table 1)^[1].

Colonic mucosal biopsies were collected before the first FMT in November 2014 and 1 mo after the second FMT in March 2015. Colonic biopsy specimens for immunological studies were taken from the hepatic flexure, and stored in PBS on ice for a maximum of 20 h until lymphocyte isolation and analysis were

done. Routine biopsy specimens were obtained from the proximal, transverse, and distal colon for histopathologic confirmation of the diagnosis. The third FMT, also with cecal instillation, was performed in May 2015.

The patient felt generally better for 2 wk after the first FMT in November 2014, without any change in the number of daily stools. After the second FMT in March 2015, the patient felt an improvement with loose rather than watery stools for one month. The histopathology before the first transplant and after the second transplant showed typical and unaltered features of CC. After the third FMT in May 2015, remission, as defined by Hjortswang *et al.*^[21], was achieved for 11 mo, with 2 normal stools daily, and a weight gain from 48 till 55 kg. After 11 mo, the patient gradually relapsed, but has been in remission with a medication of budesonide, which did not have any effect before the FMTs. The patient have had no adverse effects from any of the FMTs. The course is summarized in Table 1.

Analysis of immunomodulatory effect of FMT using flow cytometry

The isolation of intraepithelial lymphocytes (IELs) and lamina propria lymphocytes (LPLs) were performed as described in our previous study^[22]. 200000 cells/mL were stained with fluorochrome-conjugated antibodies, and corresponding fluorochrome-conjugated isotype controls were used to eliminate non-specific staining^[22]. Surface labeled cells were fixed and permeabilized using the Nuclear Factor Fixation and Permeabilization Buffer Set according to the manufacturer's instructions (Biolegend, San Diego, CA, United States) and thereafter stained with anti-Ki67-PE^[22], anti-FoxP3-PE (clone 259D/C7; BD Biosciences) or isotype control (IgG1κ-PE, BD Biosciences). A minimum of 100,000 events was collected on a Coulter Epics Altra flow cytometer (Beckman Coulter, Danvers, MA, United States) and analyzed using Kaluza software v1.3 (Beckman Coulter) based on gated CD3⁺ lymphocytes. IEL samples were only analyzed for CD3, CD4, and CD8 markers as the number of events obtained were less than 1000 for the rest of the markers^[22].

The immunomodulatory effect of FMT was assessed according to immunophenotypes of colonic mucosal T cells before the first and after the second FMTs (Table 2). Although no major changes were observed in the proportions of CD3⁺CD4⁺ and CD3⁺CD8⁺ LPLs after the second FMT, the proportion of CD4⁺ and CD8⁺ activated/memory CD45RO⁺ LPLs were decreased, whereas the proportion of CD4⁺ and CD8⁺ naïve CD45RA⁺ T cells was increased and unchanged, respectively. The proportion of proliferating CD4⁺ and CD8⁺ Ki67⁺ LPLs were increased after the second FMT. The proportion of CD4⁺ FoxP3⁺ lamina propria regulatory T cells (Treg) was increased 3.5 times after the second FMT, whereas the proportion of CD8⁺ Foxp3⁺ T cells was decreased. The proportion

Table 2 Percentages of lamina propria and intraepithelial T cell subsets expressing different markers detected by flow cytometry before and after faecal microbiota transplantation

Cell phenotype	Before first FMT	After second FMT
Percentages of lamina propria T cell subsets		
CD3 ⁺ CD4 ⁺	53.0	51.1
CD3 ⁺ CD4 ⁺ CD45RO ⁺	37.2	29.2
CD3 ⁺ CD4 ⁺ CD45RA ⁺	4.0	8.4
CD3 ⁺ CD4 ⁺ Ki67 ⁺	1.2	2.9
CD3 ⁺ CD4 ⁺ Foxp3 ⁺	2.9	10.2
CD3 ⁺ CD8 ⁺	40.7	38.9
CD3 ⁺ CD8 ⁺ CD45RO ⁺	18.8	7.4
CD3 ⁺ CD8 ⁺ CD45RA ⁺	19.5	18.1
CD3 ⁺ CD8 ⁺ Ki67 ⁺	1.2	2.9
CD3 ⁺ CD8 ⁺ Foxp3 ⁺	2.9	1.4
Percentages of intraepithelial T cell subsets		
CD3 ⁺ CD4 ⁺	13.3	22.1
CD3 ⁺ CD8 ⁺	77.9	62.4

FMT: Faecal microbiota transplantation.

of CD3⁺CD8⁺ IELs was decreased after the second FMT, whereas the proportion of CD3⁺CD4⁺ IELs was increased.

DISCUSSION

In an earlier study, we showed that diversion of the faecal stream in CC patients led to clinical and histopathological remission indicating a possible role of luminal factors in initiating the inflammation in CC^[10]. Our observation showing that FMT can result in clinical improvement of CC, supports the hypothesis that luminal factors, including or influencing the intestinal microbiota, are involved in the pathogenesis of CC. Efficacy of FMT has been shown in ulcerative colitis^[11-14] and in recurrent infections with *Clostridium difficile* in the colon^[15-17]. Although the pathophysiological mechanisms of FMT are not known in detail, it is shown that FMT can restore a dysbiosis in the gut^[23]. The colonic microbiota in CC are reported to be disturbed^[19,20], and thus a potential target for modification by FMT. To the best of our knowledge, this is the first work demonstrating beneficial effects of FMT in the clinical management of CC.

The recorded increased proportion of CD3⁺CD8⁺ IELs compared to controls in the patient before FMT is in accordance with our previous studies in CC patients^[22,24]. This cell type was decreased after the second FMT indicating a reduction in the excessive cytotoxic activity against microbes^[4,25,26]. The increased proportions of CD3⁺CD4⁺ IELs after two FMTs indicate improved tissue repair^[27,28], which in turn may contribute to remission. The decreased proportions of CD4⁺ and CD8⁺ activated/memory CD45RO⁺ cells after the second FMT suggest reduced immune responses due to the altered microbiota^[29]. The increase in regulatory Foxp3⁺CD4⁺ cells, similarly to our and others' previous studies^[24,30], is likely important to

ameliorate the ongoing inflammation, whereas the role of Foxp3⁺CD8⁺ T cells in CC pathology remains elusive. Increased proportions of proliferating Ki67⁺ CD4⁺ LPLs after the second FMT may be due to the increased proportions of Foxp3⁺ regulatory T cells.

According to the T lymphocyte subset profile, the immune response in the mucosa was likely still activated, which may partly explain why the patient relapsed and required a third FMT to reach a long-term clinical remission. We did not collect new biopsies after the last FMT due to the risk of cleansing the colon, as the biopsies were collected from the right flexure.

In conclusion, this case study may represent a novelty in the clinical management of MC. We used FMT with a good clinical effect, and it suggests a new indication for the microbiota-related therapeutic concept. Although this is only a case-report, we believe that FMT in MC should be further studied to explore the potential of this approach.

COMMENTS

Case characteristics

A 72-year-old female who suffered from frequent watery diarrhea and was diagnosed with collagenous colitis (CC) six months after debut of symptoms in 2008.

Laboratory diagnosis

She had normal biochemical and hematologic parameters, whereas faecal calprotectin levels were increased from 160 mg/kg in 2009 to 500 mg/kg when the CC deteriorated in 2013. All stool cultures were negative for *Salmonella* species, *Shigella dysenteriae*, *Campylobacter jejuni*, *Yersinia enterocolitica* and *Clostridium difficile*.

Imaging diagnosis

The colonoscopy was normal.

Pathological diagnosis

Histopathological evaluation showed an increased number of lymphocytes in the lamina propria, in the epithelium and in a few crypts. There was a thickened collagenous band subepithelially. The findings were diffusely distributed in the whole colon.

Treatment

The patient responded only temporarily to medical treatment. Accordingly, she had repeated fecal microbiota transplantations.

Related reports

Fecal microbiota transplantation (FMT) was reported for the first time in 1958. Since then, FMT has been performed for various indications, such as *Clostridium difficile*-infection (CDI), inflammatory bowel disease, irritable bowel syndrome, and metabolic syndrome. FMT for CDI has been established as an effective therapy when compared to treatment with antibiotics. Despite dysbiosis in CC patients, FMT as a possible treatment for CC has not been reported before.

Term explanation

FMT is a process of transplantation of fecal bacteria from a healthy individual into a recipient to modify microbiota dysbiosis.

Experiences and lessons

FMT is apparently a potential treatment for refractory severe CC.

Peer-review

The manuscript from Günaltay *et al.* presents a case of a patient with collagenous colitis receiving faecal microbiota transplantation. The case is interesting and describes a novel application of a procedure already established in other conditions.

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