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Patients' views on fecal microbiota transplantation: an acceptable therapeutic option in inflammatory bowel disease?

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Background Fecal microbiota transplantation (FMT) represents a new therapeutic option that has been studied in two randomized-controlled trials in ulcerative colitis patients. Our study aimed to identify patients' views on the use of this novel therapeutic approach.

Methods Using an anonymous questionnaire, we obtained data from 574 inflammatory bowel disease (IBD) patients on their knowledge and willingness to undergo FMT.

Results A large proportion of IBD patients (53.5%) are unaware that FMT is a therapeutic option in *Clostridium difficile* infection and potentially IBD. More responders preferred FMT (31.5%) to a study with a new medication (28.9%), although the difference was not significant ($P = 0.37$), and the preferred way of transplantation was colonoscopy (49.7%). In all, 38.3% preferred a family member as a donor, but there was fear about the procedure (41.5% mentioned fear of infectious diseases, 26.5% expressed disgust). The knowledge of successful FMT treatment in other patients was important for 82.2% of responders and for 50.7%, a discussion with a specialist would likely change their opinion about FMT.

Conclusion FMT represents a therapeutic procedure that is of interest for IBD patients. As FMT has been receiving increasing interest as an alternative treatment in IBD and more studies on FMT in IBD are being carried out, it is important to learn about the knowledge, attitude, and preferences of patients to provide better education to patients on this topic. However, there are reservations because of the fact that data on the benefits of FMT in IBD are controversial and several limitations exist on the use of FMT in IBD. Eur J Gastroenterol Hepatol 29:322–330

Introduction

Environmental, genetic, and immunological factors as well as the intestinal microbiota have been considered to be major etiological factors in the pathogenesis of inflammatory bowel disease (IBD) [1]. Evidence suggests that the development of IBD is a result of an inappropriate and ongoing activation of the mucosal immune system driven by the presence of intestinal microbiota in the genetically susceptible host [2–4].

Besides IBD, infectious diseases of the bowel are also associated with diarrhea and abdominal pain. One example is *Clostridium difficile* infection (CDI). Bartlett *et al.* [5] first identified *C. difficile* as the major infectious cause of antibiotic-associated diarrhea in 1978. In the past few years, there has been a constant increase in CDI [6]. The treatment of choice is an antibiotic treatment with metronidazole or vancomycin, with clinical cure rates of 90%. An emerging therapeutic option for the treatment of CDI in recent years is fecal microbiota transplantation (FMT) and treatment guidelines have been published [7,8]. In a randomized study by van Nood *et al.* [9], the infusion of donor feces was significantly more effective for the treatment of recurrent CDI than the use of vancomycin. Because of the high efficacy of this treatment and the relatively low rate of adverse effects, FMT has gained increasing importance in the treatment of recurrent *C. difficile* colitis, with several randomized trials conducted in the past few years showing its efficacy [10–12].

In FMT, a fecal suspension from a healthy individual is infused into the gastrointestinal tract of another individual in an attempt to treat an illness. This treatment has a low complication rate; adverse effects that are most often reported are those associated with a colonoscopy. Furthermore, to date, no transmissions of infectious bowel diseases have been reported [13].

CDI has also become particularly problematic for patients with IBD, contributing to a significant burden of disease [14]. The prevalence of asymptomatic Clostridium carriage in IBD is higher and the incidence of symptomatic

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CDI has been increasing [15–17]. Furthermore, patients with IBD are at an increased risk for adverse outcomes from CDI, which can also impact the management of the underlying IBD [18]. In a recent retrospective cohort study by Razik *et al.* [19], where IBD patients with recurrent CDI were compared with those with a single episode, IBD patients were 33% more likely to experience recurrent CDI compared with the general population.

In terms of the therapy of IBD, the management of an acute flare and the maintenance of remission have to be distinguished and therapeutic options in IBD treatment include medical as well as surgical interventions [20,21]. In both settings, systemic immunosuppressive medications, such as corticosteroids or anti-tumor necrosis factor (TNF) antibodies, play an important role. However, the success of all of these therapeutic options is limited in a significant number of patients and severe side effects can occur [20,21]. Furthermore, ulcerative colitis (UC) and Crohn's disease (CD) account for considerable and growing costs to the healthcare system and society [22]. In a German study, it was shown that in the outpatient setting, drugs accounted for 85% of the total costs [23]. Therefore, the need for novel, highly efficient, and well-tolerable treatment options is obvious.

Current research has led to more and more interest on FMT for the treatment of IBD. However, data on the use of FMT in IBD are sparse, but since a first case report of FMT for UC treatment by Bennet and Brinkman [24] was published in 1989, this therapeutic option has been studied more widely. Still, the data on the benefits of FMT in UC are controversial and there are no data supporting the use of FMT in CD. In detail, Kunde *et al.* [25] carried out a single-center uncontrolled study of FMT in 10 children with UC, showing safety, tolerability, and clinical response. However, because of the small sample size and the short follow-up period of only 6 weeks, the results have to be interpreted with caution. In a recent systematic review by Ianiro *et al.* [26], summarizing the results of 133 patients with IBD who were managed with FMT, a resolution of or a reduction in symptoms was reported in 80 (71%) of 113 patients with evaluable IBD. Furthermore, recently, two randomized-controlled trials evaluated FMT in UC. In a randomized-controlled trial conducted by Moayyedi *et al.* [27], comparing FMT and placebo in active UC, of 70 patients, nine (24%) of 38 patients who received FMT and two (5%) of 37 patients who received placebo were in remission at 7 weeks, showing a statistically significant effect of FMT ($P = 0.03$), with no difference in adverse events. However, in a randomized-controlled phase 2 trial by Rossen and colleagues, comparing FMT from healthy donors to autologous fecal microbiota (control) in 50 patients with mild to moderately active UC, there was no statistically significant difference in clinical and endoscopic remission between the two groups. However, this may be because of the limited number of patients who were included in the study [28].

However, there are still several limitations in the use of FMT in IBD, but there is no standardization of FMT preparation and the ideal route and timing/duration of administration to induce and maintain a clinical response has to be further investigated. Also, the optimal choice of the donor is still unclear. Further, the use of FMT is limited to CDI by the American Food and Drug Administration; apart from CDI, an investigational new drug permit is required. FMT in IBD is also mentioned in the current international IBD treatment guidelines [20,29,30].

Despite the interest in FMT in IBD patients, this treatment approach is still underinvestigated. This is also because of the fact that respective research is restricted by regulatory agencies mainly because of concerns about the potential risks of FMT [31–34]. Further, there are no conclusive data available on whether patients would even tolerate FMT as a treatment. However, patients are actively asking for this type of treatment and, in particular, on the internet, there are 'do-it-yourself' home protocols for FMT and reports on patients' own FMT experiences performed by themselves [35,36].

Two recent studies suggested that patients would actually be very interested in performing FMT in a hospital setting as a treatment for their IBD [37,38]. Here, we aimed to assess the view of a broad number of IBD patients with respect to FMT as a potential treatment option.

Methods

Study design

The study was approved by the local ethical committees (approval number: KEK-ZH-Nr. 2013-0493 from 5 November 2013, Cantonal Ethics Committee of the Canton Zürich, Switzerland). The data were collected and analyzed anonymously. Patients were entirely recruited from Swiss Crohn's Disease and Ulcerative Colitis Patient Network (SMCCV). The SMCCV is an IBD support group with members from all parts of Switzerland. It currently includes 2237 members (which includes patients but also gastroenterologists and companies); 1828 are IBD patients. A total of 747 patients with UC and 1081 patients with CD are registered. In all, 1328 are female and 855 are male members. The study was carried out using an anonymous questionnaire that was developed specifically for this purpose. Patients who went through FMT were not excluded from the study/analyses.

Survey instrument

An anonymous questionnaire was sent to the patients of the SMCCV. An anonymous questionnaire was developed specifically for this purpose. To aid the development of the questionnaire, patient interviews in the IBD clinic of the University Hospital Zurich were performed.

At the beginning of the administration of the questionnaire, before they read an information sheet about FMT, patients were first questioned whether they had heard about FMT in the past and whether they would undergo FMT on the basis of their current state of knowledge (before reading the FMT information page, see Supplemental digital content 1, *http://links.lww.com/EJGH/A146*, Supplemental digital content 2, *http://links.lww.com/EJGH/A147*). Then, an A4 page of basic information on FMT was provided to the patients (for English translation of information sheet, see Supplementary Appendix, Supplemental digital content 3, *http://links.lww.com/EJGH/A148*). As the questionnaire was sent out by post, it could not be verified whether the patients read the FMT information page before answering the first questions. This was followed by questions on patients' demographics (year of birth, age at diagnosis, sex),

disease characteristics (type of IBD, complications such as fistula and/or bowel stenosis, history of surgery, history of medical therapy, course of the disease), their knowledge of FMT, and their views about undergoing FMT. Question formats included yes or no questions and multiple-choice questions. At the end of the questionnaire, the patients were again questioned whether they would agree to undergo FMT.

Statistical analysis

A descriptive statistical analysis was carried out. Qualitative variables were expressed as percentages, whereas quantitative variables were expressed as median. Furthermore, a statistical analysis was carried out using a two-sided Fisher's exact test (GraphPad Prism 5.04 for Windows; GraphPad Software Inc., La Jolla, California, USA).

Results

Patients' characteristics

A total of 2237 questionnaires were sent out (to all SMCCV members); only IBD patients were asked to complete the questionnaires (1828 patients). In total, we received 574 completed questionnaires, yielding a response rate of 31.4%.

Responders ranged in age from 14 to 86 years (median: 46 years). Seven patients were below 18 years of age at the time of the study. The median age at diagnosis was 29 years (1–83 years). Overall, 334 (58.2%) responders were females and 239 (41.6%) responders were males. In terms of the disease characteristics, 327 (56.9%) responders had CD, 234 (40.8%) responders had UC, and 13 (2.2%) responders did not specify what disease they had (Table 1).

In terms of previous history of surgery because of IBD, 383 (66.7%) responders had never undergone surgery and 187 (32.6%) responders had undergone one or more surgical procedures in the past. The self-reported disease severity was mild in 200 (34.9%) responders, moderate in 279 (48.6%) responders, and severe in 77 (13.4%) responders; 18 (3.1%) responders did not specify. When questioned on their quality of life, the majority of responders (370 responders, 64.4%) stated that their disease negatively influenced their daily activities, whereas in 192 (33.5%) responders, it did not. When asked to what extent the responders worried about the future course of their disease, the majority of responders (342 responders, 59.6%) worried at least a little about possible disease progression, 168 (29.3%) responders did not worry, and 61 (10.6%) responders reported considerable fear that the disease may progress. Furthermore, 72.1% of the responders (414 responders) reported worries about possible side effects of actual or future medical treatment, whereas only 154 (26.8%) responders were not worried (Table 1).

Questions on fecal microbiota transplantation

A roughly equal fraction of responders had never heard of FMT (307 responders, 53.5%), whereas 262 (45.6%) responders were aware of FMT. In all, 55.4% of the responders (318 responders) stated that they would not undergo FMT on the basis of their current state of knowledge, whereas 36.9% (212 responders) would agree to the procedure. In all, 44 (7.7%) responders did not answer the question (Table 1). When comparing CD versus UC responders, 114 of 327 CD responders and 97 of 234 UC responders stated that they would agree to FMT on the basis of their current state of knowledge, with no statistically difference between the two groups [$P = 0.12$, odds ratio (OR) = 0.75, 95% confidence interval (CI): 0.52–1.06]. Also, on comparing men versus women (OR = 1.15, 95% CI: 0.81–1.64, $P = 0.47$), mild versus severe disease (OR = 0.65, 95% CI: 0.37–1.12, $P = 0.12$), and TNF-naive versus TNF-experienced responders (OR = 1.10, 95% CI: 0.75–1.61, $P = 0.70$), there was no statistically significant difference.

When further asked about their preference between a study with a new medication or FMT, 166 (28.9%) responders preferred a study with a new medication, 181 (31.5%) responders preferred FMT, 226 (39.4%) responders were not sure about what to choose, and 17 (3%) responders did not answer the question (multiple answers possible).

We were next interested in which donor the patients would accept. The majority of responders (220 responders, 38.3%) stated that they would prefer a family member for FMT, 190 (33.1%) responders stated that they would choose the spouse/living partner, only 7% (40 responders) stated that they would pick a friend, and 35.2% (202 responders) stated that they did not care about the kind of donor. In this question, multiple answers were possible.

When asked what concerns the patient has regarding FMT (multiple answers possible), 238 (41.5%) responders mentioned fear of infectious diseases, 152 (26.5%) responders expressed disgust about the procedure, 139 (24.2%) responders stated that the estimated success rate is too low, and 147 (25.6%) responders did not know what would speak against fecal transplantation. In all, 27 (4.7%) responders did not specify.

On being asked whether their decision would be influenced in a positive way if they would know about successful FMT treatment in other patients, 472 (82.2%) responders answered that they agreed, 85 (14.8%) disagreed, and 17 (3%) responders did not specify.

Overall, 291 (50.7%) responders stated that a detailed discussion with a specialist would probably change their opinion about FMT, whereas 64 (11.2%) responders stated that this would not change their opinion and 204 (35.5%) were undecided. In all, 15 (2.6%) did not answer the question.

For the majority of responders, the preferred way of transplantation would be colonoscopy (285 responders, 49.7%), 120 (21%) responders stated that they would choose an enema, and only 29 (5.1%) responders stated that they would choose application of the FMT by nasogastric tube (NGT) placement. In all, 155 (27%) responders had no preferred route of application and 34 (5.9%) did not answer the question. In this question, multiple answers were possible.

Patients were then questioned whether, if they do agree to a FMT, they would then also agree to receive FMT by one or multiple anonymous donors. Overall, 184 (32.0%) stated that they would agree to anonymous donor(s), 181 (31.5%) stated that they would not, and 197 (34.3%) were undecided. In all, 12 (2.1%) responders did not answer the question.

Table 1. Results of the questionnaire

Questions	All responders [*n* (%)]	Crohn's disease [*n* (%)]	Ulcerative colitis [*n* (%)]
1. Did you hear about the possibility of FMT in the past? (question before FMT information sheet)			
Yes	262 (45.6)	141 (43.1)	117 (50)
No	307 (53.5)	185 (56.6)	114 (48.7)
Not specified	5 (0.9)	1 (0.3)	3 (1.3)
Total	574 (100)	327 (100)	234 (100)
2. Would you undergo FMT at your current level of knowledge? (question before FMT information sheet)			
Yes	212 (36.9)	114 (34.9)	97 (41.5)
No	318 (55.4)	189 (57.8)	120 (51.3)
Not specified	44 (7.7)	24 (7.3)	17 (7.2)
Reading of FMT information sheet			
3. Sex			
Male	239 (41.6)	197 (60.2)	131 (56)
Female	334 (58.2)	130 (39.8)	103 (44)
Not specified	1 (0.2%)	–	–
4. Age (years)	46 (14–86)	–	–
5. Diagnosis			
Crohn's disease	327 (57)	–	–
Ulcerative colitis	234 (40.8)	–	–
Not specified	13 (2.2)	–	–
6. Age at diagnosis (years)			
Median (range)	29 (1–83)	–	–
7. Previous surgeries due to IBD?			
No	383 (66.7)	166 (50.1)	207 (88.5)
1×	75 (13.1)	68 (28.7)	7 (3)
2×	41 (7.1)	30 (9.2)	11 (4.7)
3× or more	71 (12.4)	61 (18.7)	8 (3.4)
Not specified	4 (0.7)	2 (0.6)	1 (0.4)
8. Which are the current or former immunosuppressive medications you take/took?			
Steroids			
Yes	368 (64.1)	210 (64.2)	152 (65)
No	129 (22.5)	69 (21.1)	57 (24.4)
Not specified	77 (13.4)	48 (14.7)	25 (10.7)
Azathioprine/mercaptopurine/methotrexate			
Yes	344 (59.9)	216 (66.1)	123 (52.6)
No	161 (28.1)	70 (21.4)	87 (37.2)
Not specified	69 (12)	41 (12.5)	24 (10.3)
Anti-TNF therapy (infliximab/adalimumab/certolizumab-pegol)			
Yes	214 (37.3)	149 (45.6)	62 (26.5)
No	255 (44.4)	127 (38.8)	123 (52.6)
Not specified	105 (18.3)	51 (15.6)	49 (20.9)
9. How would you describe the course of your disease?			
Mild	200 (34.9)	111 (33.9)	85 (36.3)
Moderate	279 (48.6)	166 (50.8)	108 (46.2)
Severe	77 (13.4)	41 (12.5)	34 (14.5)
Not specified	18 (3.1)	9 (2.8)	7 (3)
10. Do you suffer from your disease and are you impaired in your daily life?			
No	192 (33.5)	100 (30.1)	89 (38)
Yes, a little	290 (50.5)	173 (52.9)	112 (47.9)
Yes, a lot	80 (13.9)	50 (15.3)	27 (1.2)
Not specified	12 (2.1)	4 (1.2)	6 (2.6)
11. Do you fear of the further course of your disease?			
No	168 (29.3)	99 (30.3)	68 (29.1)
Yes, a little	342 (59.6)	190 (58.1)	143 (61.1)
Yes, a lot	61 (10.6)	37 (11.3)	23 (9.8)
Not specified	3 (0.5)	1 (0.3)	
12. Are you worried about the side effects of medication you are taking at the moment or you might have to take in the future?			
No	154 (26.8)	87 (26.6)	63 (26.9)
Yes, a little	280 (48.8)	169 (51.7)	108 (46.2)
Yes, a lot	134 (23.3)	70 (21.4)	60 (25.6)
Not specified	6 (1.1)	1 (0.3)	3 (1.3)
13. Which of the following therapeutic options would you prefer? (multiple answers possible)			
Study with a new medication	166 (28.9)	92 (28.1)	71 (30.3)
Fecal transplantation	181 (31.5)	95 (29.1)	85 (36.3)
Don't know	226 (39.4)	139 (42.5)	80 (34.2)
Not specified	17 (3)	9 (2.8)	6 (2.6)
14. Who would you choose as a FMT donor? (multiple answers possible)			
Family member	220 (38.3)	131 (40.1)	87 (37.2)
Spouse/living partner	190 (33.1)	102 (31.2)	85 (36.3)
Friends	40 (7)	28 (8.6)	11 (4.7)
Doesn't matter	202 (35.2)	111 (33.4)	87 (37.2)
Not specified	49 (8.5)	26 (8)	19 (8.1)
15. What would argue against FMT for you personally? (multiple answers possible)			
Fear of infectious disease	238 (41.5)	138 (42.2)	95 (40.6)
To less successful	139 (24.2)	89 (27.2)	49 (20.9)

Table 1. (*Continued*)

Questions	All responders [*n* (%)]	Crohn's disease [*n* (%)]	Ulcerative colitis [*n* (%)]
Disgust	152 (26.5)	92 (28.1)	58 (24.8)
Don't know	147 (25.6)	78 (23.9)	63 (26.9)
Not specified	27 (4.7)	15 (4.6)	10 (4.3)
16. Would your decision be influenced if you had knowledge about successful FMT therapies in other patients?			
Yes	472 (82.2)	264 (80.7)	200 (85.5)
No	85 (14.8)	52 (15.9)	30 (12.8)
Not specified	17 (3)	11 (3.4)	4 (1.7)
17. Would a detailed discussion with a specialist change your opinion?			
Yes	291 (50.7)	161 (49.2)	125 (53.4)
No	64 (11.2)	33 (10.1)	27 (11.5)
Don't know	204 (35.5)	123 (37.6)	79 (33.8)
Not specified	15 (2.6)	10 (3.1)	3 (1.3)
18. Which of the following procedures for FMT would you prefer? (multiple answers possible)			
Nasogastric tube	29 (5.1)	25 (7.6)	3 (1.3)
Colonoscopy	285 (49.7)	157 (48)	126 (53.8)
Enema	120 (21)	57 (17.4)	60 (25.6)
Doesen't matter	155 (27)	95 (29.1)	56 (23.9)
Not specified	34 (5.9)	20 (6.1)	11 (4.7)
19. If you agree to FMT would you also agree to an anonymous donor/donors?			
Yes	184 (32.0)	99 (30.3)	83 (35.5)
No	181 (31.5)	110 (33.6)	67 (28.6)
Don't know	197 (34.3)	110 (33.6)	83 (35.5)
Not specified	12 (2.1)	8 (2.44)	1 (0.4)
20. Would you now undergo FMT with your actual state of knowledge?			
No	92 (16)	53 (16.2)	36 (15.4)
Yes	191 (33.3)	101 (30.9)	89 (38)
Yes, as the last option	154 (26.8)	94 (28.7)	60 (26.6)
Don't know	128 (22.3)	75 (22.9)	47 (20.1)
Not specified	9 (1.6)	4 (1.2)	2 (0.9)
21. Do you feel confident about your decision to possibly undergo FMT?			
Yes	255 (44.4)	138 (42.2)	114 (48.7)
No	282 (49.1)	166 (50.8)	111 (47.4)
Not specified	37 (6.5)	23 (7)	9 (3.9)
22. Are you aware of the advantages and disadvantages of FMT?			
Yes	260 (45.3)	141 (43.1)	117 (50)
No	278 (48.4)	164 (50.2)	106 (45.3)
Not specified	36 (6.3)	22 (6.7)	11 (4.7)
23. Are you aware of the advantages and disadvantages that are the most important for you?			
Yes	289 (50.4)	161 (49.2)	127 (54.3)
No	251 (43.7)	145 (44.3)	98 (41.9)
Not specified	34 (5.9)	21 (6.4)	9 (3.8)
24. Did you get enough support and advise to make your decision?			
Yes	196 (34.1)	111 (33.9)	83 (35.5)
No	338 (58.9)	197 (60.2)	134 (57.3)
Not specified	40 (7)	19 (5.8)	17 (7.3)

FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

The patients were again asked whether they would undergo FMT after reading the Information sheet about FMT and after answering the previous 19 questions. The majority of responders (345 from 574, 60.1%) agreed to FMT [including 191 (33.3%) responders who agreed to FMT and 154 (26.8%) responders who would agree to FMT, but only as the last therapeutic option], whereas 92 (16%) responders stated that they would not. In all, 128 (22.3%) were undecided and nine (1.6%) responders did not answer the question. Interestingly, there was a change in the decision on FMT (Fig. 1 and Table 1).

When comparing CD versus UC responders, 195 of 327 CD responders and 149 of 234 UC responders stated that they would agree to FMT at the end of the questionnaire, with no statistically difference between the two groups (OR = 0.89, 95% CI: 0.55–1.43, $P = 0.72$). Also, when comparing men versus women (OR = 1.21, 95% CI: 0.76–1.94, $P = 0.48$) and patients with mild versus severe disease (OR = 0.71, 95% CI: 0.34–1.47, $P = 0.38$), there was no statistically significant difference. TNF-naive versus TNF-experienced responders were also compared (Fig. 2).

This result was also analyzed in a subgroup analysis of CD versus UC responders (Figs 3 and 4).

The majority of responders did not feel sure (282 responders, 49.1%) about their decision to undergo FMT, whereas 255 (44.4%) felt sure with their decision and 37 (6.5%) responders did not specify.

In terms of the awareness of the advantages and disadvantages of FMT, 260 (45.3%) responders stated that they were aware of the advantages and disadvantages, whereas 278 (48.4%) stated that they were not. In all, 36 (6.3%) responders did not specify. Furthermore, the majority of responders (289, 50.4%) stated that they were sure about which advantages and disadvantages are the most important for themselves, whereas 251 (43.7%) responders stated that they were not. In all, 34 (5.9%) responders did not specify.

Finally, the patients were asked whether they had enough support and advice to make a decision about FMT. Overall, 196 (34.1%) responders agreed that they had enough support/advice for their decision, whereas 338 (58.9%) responders stated that they did not. In all, 40 (7%) responders did not specify (Table 1).

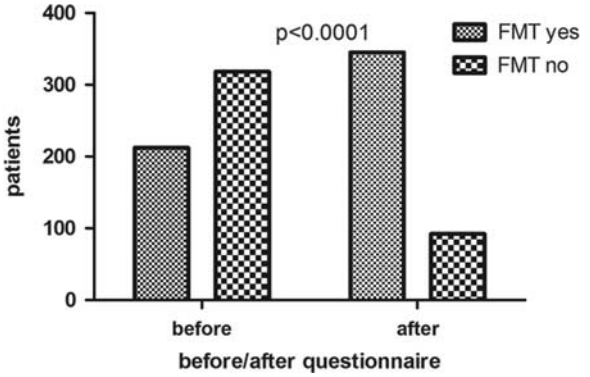

Fig. 1. The proportion of all responders agreeing to FMT before and after reading the questionnaire. When comparing the view of patients on FMT at the beginning versus the end of the questionnaire, at the end of the questionnaire, a significantly higher proportion of all responders agreed to FMT compared with the beginning of the questionnaire (345 vs. 212 responders) (OR = 0.18, 95% CI: 0.13–0.24, $P < 0.0001$). CI, confidence interval; FMT, fecal microbiota transplantation; OR, odds ratio.

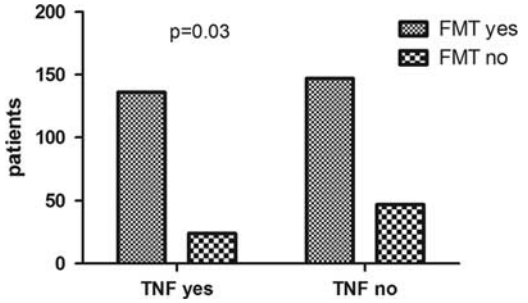

Fig. 2. The proportion of TNF/TNF-naive responders agreeing to FMT after reading the questionnaire. When comparing TNF-naive versus TNF-experienced responders, statistically more TNF-experienced responders stated that they would agree to FMT after reading the questionnaire compared with responders without TNF therapy (OR = 1.81, 95% CI: 1.05–3.12, $P = 0.03$). CI, confidence interval; FMT, fecal microbiota transplantation; OR, odds ratio; TNF, tumor necrosis factor.

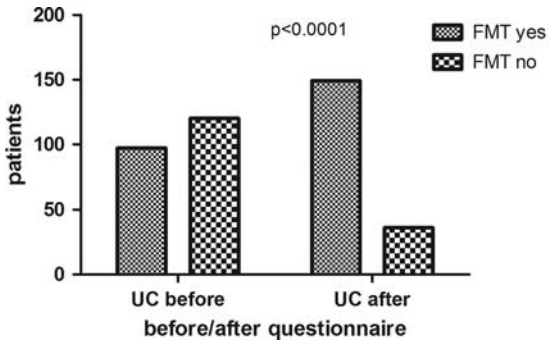

Fig. 3. The proportion of UC responders agreeing to FMT before and after reading the questionnaire. In a subgroup analysis of CD versus UC responders, in the UC group, significantly more responders (149 of 234 responders) stated that they would agree to FMT at the end of the questionnaire compared with the beginning (97 of 234 responders) (OR = 0.20, 95% CI: 0.12–0.31, $P < 0.0001$). CD, Crohn's disease; CI, confidence interval; FMT, fecal microbiota transplantation; OR, odds ratio; UC, ulcerative colitis.

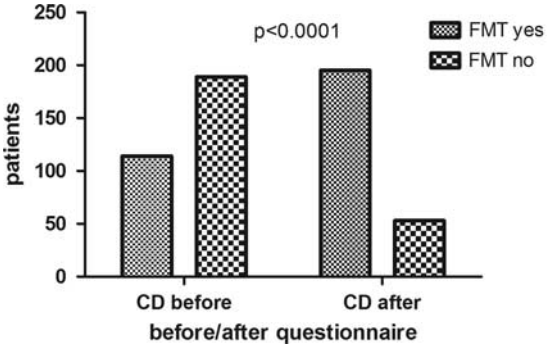

Fig. 4. The proportion of CD responders agreeing to FMT before and after reading the questionnaire. In a subgroup analysis of CD versus UC responders, in the CD group, significantly more responders (195 of 327 responders) stated that they would agree to FMT at the end of the questionnaire compared with the beginning (114 of 327 responders) ($P < 0.0001$, OR = 0.16, 95% CI: 0.41–0.56). CD, Crohn's disease; CI, confidence interval; FMT, fecal microbiota transplantation; OR, odds ratio; UC, ulcerative colitis.

Discussion

Using data from 574 patients of the SMCCV, we showed that FMT might be accepted as a therapeutic option by many IBD patients. The majority of the patients, 60.1%, who took part in our survey stated that they would undergo FMT, 44.6% of these only as the last therapeutic option. Moreover, when questioned about their preferences between a study with a new medication or FMT, more patients stated that they would prefer FMT (31.5%) compared with a study with a new medication (28.9%), although the difference was not significant (OR = 0.88, 95% CI: 0.69–1.14, $P = 0.37$). This is of particular interest and might be because of the fact that FMT might be considered a 'natural' treatment with possibly foreseeable side effects in contrast to the treatment with a novel, likely 'unnatural' molecule exerting possibly unforeseeable risks. However, to date, the long-term effects after FMT are not known.

Different routes of administrations for FMT are currently being studied (oral capsules, NGT, enema, or by colonoscopy) [39,40]. To date, the best route of administration has not been established. In terms of recurrent CDI, a meta-analysis by Postigo and Kim [41] showed that despite procedural differences, FMT by colonoscopy or NGT appeared to be highly effective and safe for the management of recurrent CDI, whereas other studies suggested that lower gastrointestinal FMT delivery leads to a trend toward higher clinical resolution rates than the upper gastrointestinal route [42,43]. In IBD, no studies comparing the different procedures have been carried out until now. In our study, 49.7% of the responders chose colonoscopy as the preferred route, even though this procedure was the most time consuming and complex, compared with an application by NGT or enema. Only 5.1% stated that they would choose application of FMT by NGT. This is probably because the idea of receiving FMT by the oral route is not appealing, which is underlined by the fact that 26.5% of the patients in our study expressed disgust about the procedure as a reason for not receiving FMT. It has to be noted that in some cases of IBD, some routes of delivery may be more suitable (e.g. small intestinal CD). Because the information sheet was only one page long and because of the fact that such in-depth information would be beyond the depth of information that can be passed on to somebody by a short written information sheet, we did not include this topic in the information sheet.

To date, there are no data available on what kind of donor might be best for FMT in IBD patients. It is proposed that the development of IBD is a result of an inappropriate and ongoing activation of the mucosal immune system, driven by the presence of intestinal microbiota. In our study, the majority of patients (38.3%) stated that they would choose a family member. It is questionable whether this is the best donor in the setting of IBD. For instance, it is known that the microbiome is similar in co-habiting individuals and family members [44,45]. In a recently published randomized-controlled trial comparing FMT and placebo in active UC, the kind of donor seemed to affect the outcome of FMT. The study was carried out with six different donors. Although a response rate of 7/18 (39%) was obtained for one single donor, the response rate for the other donors was only 2/20 (10%). Also, there was a statistically significant effect of the active therapy group being more similar to their donor than a control fecal sample [27]. Therefore, transferring a very similar intestinal microbiome might limit the success of FMT. The fact that the kind of donor seems to have an impact on the outcome of FMT in IBD was not mentioned in the information sheet; therefore, this additional information could have changed the patients' decision on the kind of donor that the patient would accept.

When questioned about being sure about their decision to undergo FMT, the majority of patients stated that they were unsure about their decision (49.1%). This is most probably because of the fact that a written questionnaire only includes limited information compared with discussion with a specialist. This is underlined by the fact that 48.4% of the patients stated that after completing the questionnaire, they were not aware of the advantages and disadvantages of FMT. Furthermore, 58.9% answered that they did not have enough support and advice to make a decision. This shows that only written information is not enough to enable a patient to make a decision about treatment options and a direct physician-to-patient contact is essential to build up a level of confidence, especially for this type of treatment. This is also underlined by the fact that the majority of patients (50.7%) stated that a detailed discussion with a specialist would probably change their opinion about FMT. However, further understanding of the knowledge, attitude, and behavior of specialist toward FMT is needed.

Interestingly, no significant differences were observed between women and men, UC and CD patients, or patients with a mild or a severe disease course. However, significantly more TNF-experienced patients agreed to undergo FMT after completing the questionnaire compared with TNF-naive patients. This suggests that patients who are more therapy experienced could be more interested in FMT. However, one would expect this to correlate with the comparison of a mild versus a severe disease course of IBD as patients with a severe disease course may have a higher probability of being TNF experienced. Unfortunately, when comparing the patients with a mild versus a severe disease course, we could not find a statistically significant difference ($P = 0.38$). This may be because of the fact that many physicians use anti-TNF treatments earlier in the disease course (a so-called 'top-down' therapy). Furthermore, the question on the disease course was answered by a patient who may not have been subjected to a direct comparison of his/her own disease course with other patients. Also, we lack information on whether the TNF-experienced patients responded to anti-TNF therapy or whether they were nonresponders (primary nonresponders or secondary loss of response); this information may have had an impact on the results of our study. The fact that we could not observe differences between UC and CD patients is probably because of the lack of an explanation on the current differences between CD and UC in the information sheet in terms of published evidences on FMT.

Furthermore, significantly more patients mentioned that they would consider FMT as a possible treatment option after reading the one-page patient information and completing the questionnaire. This suggests that patients might indeed be highly interested in FMT as a novel IBD treatment, but are currently lacking sufficient information on how it is performed and its possible risks and benefits.

Our study has several strengths, but also limitations. We have presented the data from a large cohort of 574 IBD patients. A major strength is that the data have been gathered prospectively. Further, because of the fact that the data have been obtained from patients who are part of a nationwide patient support group, our data not only reflect the findings of tertiary referral centers but rather those from a general population. The response rate of our questionnaire was 31.4%. This study represents the first analysis of our group within the SMCCV. Another analysis of our group in the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), which was published recently, investigated pain in IBD [46]. In this study, we had a higher response rate of 59%. The higher response rate in this cohort may be because of the fact that patients of the SIBDCS are used to receiving follow-up questionnaires on a yearly basis and are reminded to send the questionnaire back if there is no reply. This does not apply to the SMCCV. Furthermore, pain might be a bigger issue for IBD patients, given the fact that 71% of patients reported pain in the SIBDCS. However, it is noteworthy that patients filled out the questionnaire anonymously and were not in the real situation of decision making about possible FMT, making it only a hypothetical option. In the actual situation, their decision may be different. In addition, FMT is still at an experimental stage for IBD and has not found its way into the different international treatment recommendations for IBD and is not approved, apart from CDI, by the Food and Drug Administration [20,29,30]. In addition, considering that for a majority of patients a detailed discussion with a specialist is of great importance for the decision making in terms of FMT, further understanding of the knowledge, attitude, and behavior of specialists toward FMT is needed. Furthermore, patients who had undergone FMT were not excluded from the study/analyses; we, therefore, do not have information on the number and the outcome of FMT in these patients. However, as FMT is not approved as a treatment option for IBD in Switzerland, we do not believe that this aspect affects the results of our analysis. Another limitation of the study is that we did not include capsules as an option for FMT. Considering that capsules (besides NGT) represent another alternative administration route of FMT through the oral route as an alternative to the lower gastrointestinal route, inclusion of this alternative could have

influenced the outcome of our study. Also, we used a nonvalidated questionnaire for our study.

In summary, we have shown that FMT represents a therapeutic procedure that is of interest for patients with IBD. The knowledge of successful FMT treatments in other IBD patients is very important for the patients and a detailed discussion with a specialist seems to be important for the decision making on FMT. As FMT is receiving increasing attention as an alternative treatment in IBD and more studies on FMT in IBD are being carried out, it is important to determine the knowledge, attitude, and preferences of patients and healthcare providers to provide better education on this topic. However, there are reservations because of the fact that FMT is only an experimental treatment option in IBD and several limitations on the use of FMT in IBD exist.

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Conflicts of interest

There are no conflicts of interest.

References

1 Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; 448:427–434.
2 Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002; 347:417–429.
3 Cammarota G, Ianiro G, Cianci R, Bibbo S, Gasbarrini A, Curro D. The involvement of gut microbiota in inflammatory bowel disease pathogenesis: potential for therapy. *Pharmacol Ther* 2015; 149:191–212.
4 Serban DE. Microbiota in inflammatory bowel disease pathogenesis and therapy: is it all about diet? *Nutr Clin Pract* 2015; 30:760–779.
5 Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N Engl J Med* 1978; 298:531–534.
6 Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in *Clostridium difficile* infection incidence among hospitalized adults in the united states: 2001–2010. *Am J Infect Control* 2014; 42:1028–1032.
7 Bakken JS, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, *et al*. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011; 9:1044–1049.
8 Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases. European society of clinical microbiology and infectious diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* 2014; 20 (Suppl 2):1–26.
9 van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, *et al*. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; 368:407–415.
10 Cammarota G, Masucci L, Ianiro G, Bibbo S, Dinoi G, Costamagna G, *et al*. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2015; 41:835–843.
11 Lee CH, Steiner T, Petrof EO, Smieja M, Roscoe D, Nematallah A, *et al*. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection: a randomized clinical trial. *JAMA* 2016; 315:142–149.
12 Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, *et al*. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* infection: a randomized trial. *Ann Intern Med* 2016; 165:609–616.
13 Kerman DH. Endoscopic delivery of fecal biotherapy in inflammatory bowel disease. *Gastrointest Endosc Clin N Am* 2016; 26:707–717.
14 Rao K, Higgins PD. Epidemiology, diagnosis, and management of *Clostridium difficile* infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2016; 22:1744–1754.
15 Clayton EM, Rea MC, Shanahan F, Quigley EM, Kiely B, Hill C, *et al*. The vexed relationship between *Clostridium difficile* and inflammatory bowel disease: an assessment of carriage in an outpatient setting among patients in remission. *Am J Gastroenterol* 2009; 104: 1162–1169.
16 Hourigan SK, Chirumamilla SR, Ross T, Golub JE, Rabizadeh S, Saeed SA, *et al*. *Clostridium difficile* carriage and serum antitoxin responses in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; 19:2744–2752.
17 Bossuyt P, Verhaegen J, van Assche G, Rutgeerts P, Vermeire S. Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease. *J Crohns Colitis* 2009; 3:4–7.
18 Goodhand JR, Alazawi W, Rampton DS. Systematic review: *Clostridium difficile* and inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; 33:428–441.
19 Razik R, Rumman A, Bahreini Z, McGeer A, Nguyen GC. Recurrence of *Clostridium difficile* infection in patients with inflammatory bowel disease: the Recidivism Study. *Am J Gastroenterol* 2016; 111:1141–1146.
20 Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; 6:991–1030.
21 Dignass A, van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, *et al*. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010; 4:28–62.
22 Burisch J, Jess T, Martinato M, Lakatos PL. ECCO – EpiCom. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis* 2013; 7:322–337.
23 Ebinger M, Leidl R, Thomas S, Von Tirpitz C, Reinshagen M, Adler G, *et al*. Cost of outpatient care in patients with inflammatory bowel disease in a German University Hospital. *J Gastroenterol Hepatol* 2004; 19:192–199.
24 Bennet JD, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora. *Lancet* 1989; 1:164.
25 Kunde S, Pham A, Bonczyk S, Crumb T, Duba M, Conrad H Jr, *et al*. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013; 56:597–601.
26 Ianiro G, Bibbò S, Scaldaferri F, Gasbarrini A, Cammarota G. Fecal microbiota transplantation in inflammatory bowel disease: beyond the excitement. *Medicine (Baltimore)* 2014; 93:e97.
27 Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, *et al*. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology* 2015; 149:102.e6–109.e6.
28 Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, *et al*. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology* 2015; 149:110.e4–118.e4.
29 U.S. Department of Health and Human Services. Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat *Clostridium difficile* infection not responsive to standard therapies: draft guidance for industry; 2013. Available at: *http://www.fda.gov*. [Accessed 16 August 2016].
30 Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, *et al*. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto Consensus. *Gastroenterology* 2015; 148:1035.e3–1058.e3.

31 Brandt LJ. Editorial commentary: fecal microbiota transplantation: patient and physician attitudes. *Clin Infect Dis* 2012; 55: 1659–1660.
32 McKenna M. Swapping germs. *Sci Am* 2011; 305:36.
33 Floch MH. Fecal bacteriotherapy, fecal transplant, and the microbiome. *J Clin Gastroenterol* 2010; 44:529–530.
34 Hedge DD, Strain JD, Heins JR, Farver DK. New advances in the treatment of *Clostridium difficile* infection (CDI). *Ther Clin Risk Manag* 2008; 4:949–964.
35 No authors listed. Fecal flora replacement protocol. Healed of ulcerative colitis within 24 hours; 2005. Available at: *http://curezone.com/forums/fm.asp?i=57263*. [Accessed 16 August 2016].
36 Facebook discussion group. Fecal bacteriotherapy is 'the bomb'; 2012. Available at: *http://www.facebook.com/pages/Fecal-Bacteriotherapy-is-The-Bomb/183707615019796* [Accessed 16 August 2016].
37 Kahn SA, Vachon A, Rodriquez D, Goeppinger SR, Surma B, Marks J, *et al*. Patient perceptions of fecal microbiota transplantation for ulcerative colitis. *Inflamm Bowel Dis* 2013; 19:1506–1513.
38 Kahn SA, Gorawara-Bhat R, Rubin DT. Fecal bacteriotherapy for ulcerative colitis: patients are ready, are we? *Inflamm Bowel Dis* 2012; 18:676–684.
39 Hirsch BE, Saraiya N, Poeth K, Schwartz RM, Epstein ME, Honig G. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent *Clostridium difficile* infection. *BMC Infect Dis* 2015; 15:191.
40 Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA* 2014; 312:1772–1778.
41 Postigo R, Kim JH. Colonoscopic versus nasogastric fecal transplantation for the treatment of *Clostridium difficile* infection: a review and pooled analysis. *Infection* 2012; 40:643–648.
42 Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013; 108:500–508.
43 Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. *J Clin Gastroenterol* 2014; 48:693–702.
44 Song SJ, Lauber C, Costello EK, Lozupone CA, Humphrey G, Berg-Lyons D, *et al*. Cohabiting family members share microbiota with one another and with their dogs. *Elife* 2013; 2:e00458.
45 Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, *et al*. Human gut microbiome viewed across age and geography. *Nature* 2012; 486:222–227.
46 Zeitz J, Ak M, Muller-Mottet S, Scharl S, Biedermann L, Fournier N, *et al*. Pain in IBD patients: very frequent and frequently insufficiently taken into account. *PLoS One* 2016; 11:e0156666.