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FECAL TRANSPLANTATION INDICATIONS IN ULCERATIVE COLITIS. PRELIMINARY STUDY

MIHAELA LASZLO[1,3], LIDIA CIOBANU[1,2], VASILE ANDREICA[1,2], OLIVIU PASCU[1,2]

[1]Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania
[2]Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3]Gastroenterology and Hepatology Medical Center, Cluj-Napoca, Romania

Abstract

Background and aims*. Fecal microbiota transplantation is used with success in persistent (more than two episodes) Clostridium Difficile Infection; it has also gained importance and started to be used in inflammatory bowel disease. There are theoretical arguments that justify its use in ulcerative colitis or Crohn's disease. Based on our clinical cases we tried to evaluate the indications of fecal microbiota transplantation young patients with ulcerative colitis and multiple relapses, in which biological or immunosuppressive treatment were ineffective.*

Methods. *Five patients with moderate-severe ulcerative colitis or Clostridium Difficile infection who ceased to have a therapeutic response to biological therapy, were given fecal microbiota transplant as an alternative to biological therapy and/or immunosuppression. Fecal microbiota transplant was administered via colonoscopy using healthy donors from their family.*

Results*. The results were favorable and spectacular in all patients and complete remission was achieved for at least 10 months. Clinical remission was achieved in all patients. Endoscopic appearance of ulcers in patients improved. In 2 patients the effect of the fecal microbiota transplant diminished after 10-12 months and the tendency to relapse appeared (3-4 stools/day, blood streaks present sometimes in the stool). Reintroduction of systemic therapy or immunosuppression demonstrated that patients regained the therapeutic response to these treatments, and remission was maintained.*

Conclusion. *Fecal microbiota transplantation can be used as salvage therapy in patients refractory to biological therapy, as elective therapy in clostridium difficile infection or as an alternative therapy in young patients with multiple relapses who have reservations regarding biological or immunosuppressive treatment.*

Keywords: ulcerative colitis, fecal transplantation, clostridium difficile, biological therapy

Background and aims

The bacterial population in the colon is extremely large, containing 10-14 microbial cells with over 3 million bacterial genes. The total microbial population in the gut is defined as microbiota. Interestingly, Bacteroides, Faecalibacterium and Bifidobacterium are the most abundant genera, but their relative abundance is highly variable across individuals [1,2]. Bacteria play an essential role in the initiation and perpetuation of gut inflammation in inflammatory bowel disease with evident particularities between Crohn disease and ulcerative colitis. It is known that in the ulcerative colitis a dysbiosis is present, an imbalance in the gut microbiota [3] and it is clear that this imbalance leads to an improper communication between the bacteria and the immune system of the colon mucosa. Changing the composition of the intraluminal bacteria induces proinflammatory stimuli, responsible for the

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Address for correspondence: miham83@yahoo.com

characteristic mucosal lesions in ulcerative colitis [4].

Preliminary study

Recent research shows that dysbiosis in ulcerative colitis is characterized by the decreased concentration of butyrate-producing bacteria such as Roseburia Hominis and Faecalibacterium Prausnitzii, both from the (phylum) Firmicutes division [5].

Given these theoretical arguments several studies evaluate the effect of fecal microbiota transplantation in inflammatory bowel disease. The results are contradictory, but it is noted that the positive effects are present, especially in patients with ulcerative colitis [6-8].

Under these conditions we attempted to evaluate the effect of fecal microbiota transplantation in patients with ulcerative colitis and also to evaluate indications of fecal microbiota transplant in ulcerative colitis, thus answering the question whether fecal microbiota transplantation is a therapeutic alternative or should be reserved only for certain patients.

Material and methods

Patients

Of 28 patients with fecal microbiota transplantation who tested positive for Clostridium Difficile (toxins A and B positive) and ulcerative colitis in the year 2014, we selected five patients with ulcerative colitis aged between 26 - 61 years; the majority were male with extended colitis or pancolitis and more than 2 years from diagnosis (Table I).

All patients signed an informed consent and the procedure was approved by the Ethics Committee of the Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca (IRGH).

The initiation of fecal microbiota transplant was justified by the response loss to biological therapy in 3 cases, Clostridium Difficile infection, immunosuppression, or biological therapy refusal (Table II).

Table I. Clinical and demographic characteristics of patients.

Patient no.	Sex	Age	Disease duration (years)	Disease extent	Smoker	Weight (kg)	Primary treatment before fecal microbiota TRANSPLANT	Treatment duration with Infliximabum (months)	Acute disease duration (weeks)	Endoscopic Mayo score	FECAL microbiota transplant Treatment justification
1	M	61	4	extensive left colitis	No	71	Infliximab	17	4	3	Low levels of Infliximab
2	M	28	2	pancolitis	No	68	Infliximab	19	8	2	Infliximab antibodies
3	M	53	3	left colitis	No	90	Infliximab	21	4	2	Infliximab antibodies
4	F	42	4	pancolitis	no	85	Azathioprine	none	8	3	Clostridium Difficile
5	M	26	2	left colitis	No	75	5Acityl salisylic acid	none	5	2	Azathioprine or Infliximab refusal

Table II. Active spurt characteristics in fecal microbiota transplant patients.

Patient no.	No. of stools / day	Pathologic products in stool	Erythrocyte sedimentation rate mm/h	C-reactive protein mg/dl (N= 0-1mg/dl)	Hemoglobin g/dl
1	5-6	Blood and mucus	70	3.7	10.4
2	6-7	Blood	40	2	15
3	5-6	Blood	60	3	14
4	8-10	blood	136	15	13.5
5	3-4	Mucus	40	2	13

Patients:

- 1 patient with ulcerative colitis with low levels of Infliximab at 7 weeks from administration in which decreased administration interval had no effect;
- 2 patients with Infliximab antibodies;
- 1 female patient with active spurt (8-10 stools/ day, blood streaks, abdominal pain) and superinfection Clostridium Difficile infection (A and B positive toxins to patient with ulcerative colitis);
- 1 young patient with moderate-severe ulcerative colitis who had refused immunosuppressive and biological treatment.

Patients and donors were informed about the potential risks and benefits of fecal microbiota transplant and experimental status. All patients and donors gave their written informed consent prior to fecal microbiota transplant.

Donors were selected from the families of patients, first degree relatives who were tested according to the protocol.

Donor stool screening: ova and parasites, stool culture **(**Salmonella, Shigella, Escherichia coli, Yersinia enterocolitica, and Campylobacter*),* Clostridium Difficile toxins A and B, Giardia antigen**. Donor serum screening:** HIV-1 and HIV-2, Hepatitis A, B, and C, some practitioners additionally screen for: rapid plasma reagin and fluorescent treponema antibody-absorbed Treponema pallidum.

Additional potential exclusions should include donors with a history of incarceration, tattoo or body piercing in the past 6 months, current or known exposure to a communicable disease, use of immunosuppressant agents, or antibiotics within the last 3 months. Travel within the past 6 months to an area known to be a risk factor for diarrheal illness or other infectious diseases should also be considered in the analysis of donors.

Fecal suspension (~150 ml) was diluted in 0.9% sterile saline solution up to a volume of 400-425 ml. Subsequently the suspension was filtered several times. This suspension was poured into a sterile vial and administered within one hour. Donated stool is mixed with diluent to a consistency that can be injected via the biopsy channel of a colonoscopy. Before aspiration into a syringe, the suspension is filtered through gauze pads or strainer to remove large particulate matter. The administration method was transcolonic during colonoscopy, after standard preparation (Fortrans split - in doses that varied according to each patient's bowel transit). Colonoscopy offers the advantage of allowing direct colonic mucosa and evaluation, assessment of disease severity and exclusion of coexisting pathological conditions.

The patients received 4 mg of loperamide in order to reduce gut motility immediately after fecal microbiota transplant and 6 hours after the procedure. Patients received a normal diet after about 5 hours. Serological tests were evaluated every day. The day after the fecal microbiota transplant the patients were discharged.

Evaluations:

a) Clinical remission: disappearance of symptoms (pain, abdominal discomfort), the decrease in the number of stools, stool normalization, the disappearance of pathological products in the stool (mucus, blood);

b) Biological remission: Erythrocyte sedimentation rate, White blood cell, C-reactive protein;

c) Endoscopic remission: Mayo score reduction (of at least 3 points) or mucosal healing installation.

Results

Fecal microbiota transplantation using colonoscopy was performed in all patients. Mild to moderate abdominal pain was observed in the first 2 hours after transplantation, but did not require any medication. Post-procedure evolution was favorable immediately. Clinical parameters which were observed are described in Table III.

Table III. Patient characteristics 5 months after fecal microbiota transplantation.

Patient no.	No. of stools / day	Pathological products in stool	Erythrocyte sedimentation rate mm/h	C-reactive protein mg/dl (N= 0-1mg/dl)	Hemoglobin g/dl	Endoscopic evaluation
1	1-2/day	normal	29	0.37	13	Sigma and rectum edema, erythema, without vascular drawing
2	1-2/day	normal	10	0.40	15	Sigma and rectum with normal mucosa
3	2-3/day	Blooding streaks	40	0.43	14	Rectum with erased vascular drawing and edema
4	1-2/day	normal	10	1.8	13,8	Sigma and rectum with normal mucosa
5	1-2/day	normal	10	0.40	14	Sigma and rectum with normal mucosa

Clinical remission was achieved in all patients. One patient presented mild rectal bleeding, for this reason two months after fecal microbiota transplantation the decision to reintroduce Azathioprine treatment was taken. For 2 patients the 5 Acetyl salicylic acid dose was decreased to 1g/day, and the evolution was favorable. Endoscopic appearance of ulcers improved. Patients 1 and 3 were free of ulcerations, mucosal healing was found in patients 2 and 5 (Table III).

We watched using the t test and significance of C-reactive protein value before and after fecal microbiota transplant (Table IV). Since the results were statistically significant this would further support the research hypothesis.

Evolution after treatment

Cases 2, 4 and 5 had a sustained therapeutic effect, clinical and biological remission was maintained even after 1 year from fecal microbiota transplant.

Case 1 responded for 10 months when a mild activity spurt appeared. Biologic therapy was reintroduced (Infliximab) with favorable outcome administered at 8-10 weeks interval depending on colonic transit (the patient decided the optimal administration interval).

Case 3 had an incomplete remission (2-3 stools/ day, blood streaks present sometimes in the stool), for this reason Azathioprine was reintroduced. One year after fecal microbiota transplant, under Azathioprine, the patient presented 2 stools/day, without blood streaks.

Table IV. The statistical value on reducing inflammation (C-reactive protein).

	Patient						The mean (X_1, X_2 X_1, X_2)	Standard deviation	Number of freedom degrees
	1	2	3	4	5				
C-reactive protein samples - BEFORE	3.7	2	3	15	2	Calculation	5.14	5.5586	4
C-reactive protein samples - AFTER	0.37	0.40	0.43	1.8	0.40		0.68	0.6265	4

T Test Value = 1.7828.
I found P Value is <0.00001. The result of this test is significant at $p < 0.05$

Discussion

Current therapeutic methods achieve control in most cases. The appearance of biological therapy has achieved deep remission and mucosal healing in a significant number of cases. However, there are patients in which biological therapy is not effective and particularly the loss of therapeutic effect in a significant percentage of patients after a variable period of time has been described. Loss effect is due to either low levels of Infliximab, or the appearance of antibodies against the biological treatment. The remedy is to increase the dose, shorten the dosing intervals or treatment change (Adalimumab after Infliximab). fecal microbiota transplant has a theoretical justification in ulcerative colitis [8,9].

In these conditions we tested the efficiency of fecal microbiota transplantation in 3 patients who had lost the therapeutic effect due to insufficient dose (1 patient) or antibody development (2 patients). The results were spectacular. Patients entered clinical remission immediately, remission was maintained in one case until the writing of this article and for two other cases for 10-12 months. The reintroduction of biological treatment or Azathioprine for the 2 cases mentioned above proved to have a profound effect on maintaining remission duration and treatment effect was regained.

Our results show that fecal microbiota transplantation may be considered as a necessary rescue therapy in the loss of therapeutic effect for biological therapy. Of course there is also the possibility to switch to another biological treatment with durable results but only after a period of several wash-out weeks, in our patients we could not afford to lose the time as patients were in a prolonged acute spurt. A number of cases have been published in China, where clinical remission in 70% of patients achieved long term remission [10]. The female patient with Clostridium Difficile superinfection had a moderate-severe activity spurt with 8 stools/day and long term biological parameters (Erythrocyte sedimentation rate and C-reactive protein) severely altered. The superinfection of the clostridium difficile infection had occurred during the active spurt for which biological therapy was programmed. The superinfection clostridium difficile infection finding determined us to apply fecal microbiota transplant. After fecal microbiota transplant treatment pathological stools disappeared within the next day and complete remission was maintained for 5 months. For Clostridium Difficile infection it is very well known that fecal microbiota transplantation is an effective therapy [11,12] and its association with the spurt activity can be considered the indication of choice

for fecal microbiota transplantation, although results in literature are contradictory (positive results or ulcerative colitis reactivation) [13,14].

The 5th patient was a 26 year old male who had colitis and multiple moderate spurts. He had serious doubts regarding biological and immunosuppressive therapy. He opted for fecal microbiota transplantation. The results were excellent and the patient has been in complete remission for more than 2 years. In this case fecal microbiota transplant was a therapeutic alternative that could be considered in young patients who refuse aggressive treatments: immunosuppression or biological therapy.

Although encouraging our results were obtained on a small number of cases. But this diversity can provide an insight into the main indications of fecal microbiota transplantation in ulcerative colitis.

Conclusions

Fecal microbiota transplantation in ulcerative colitis is postulated to be safe and justified [6,15]. Its role in the therapeutic arsenal is still to be evaluated [15].

In our study we identified several cases in which it can be used: the loss of therapeutic effect for biological medication through under dosing or the appearance of antibodies may be an indication for salvage therapy using fecal microbiota transplant. In these cases the effects were favorable and long term remission was achieved. When the fecal microbiota transplant effect diminished we discovered that biological and immunosuppressive therapy response was achieved again.

Fecal microbiota transplant is the choice when superinfection of the clostridium difficile infection is present.

Finally, for patients, especially young patients who refuse aggressive treatments, fecal microbiota transplantation can be considered as a therapeutic alternative.

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