Contemporary Clinical Trials Communications 1 (2015) 39–41

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Treating *Clostridium difficile* infections: Should fecal microbiota transplantation be reclassified from investigational drug to human tissue?☆

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ARTICLE INFO

Article history:
Received 23 October 2015
Received in revised form
4 November 2015
Accepted 12 November 2015
Available online 1 December 2015

Keywords:
Clostridium
Difficile
FMT

ABSTRACT

Fecal microbiota transplantation (FMT) has emerged as a highly effective treatment for *Clostridium difficile* infection (CDI), the most frequent cause of hospital-acquired infectious diarrhea in developed countries and the cause of nearly 30,000 annual deaths in the US. FMT is proving to be more effective at treating CDI than traditional antibacterial therapy, and reduces the exposure of valuable antibiotics to potential resistance. A systematic review to assess the efficacy of FMT for CDI treatment showed that across all studies for recurrent CDI, symptom resolution was observed in 85% of patients. The United States Food and Drug Administration currently classifies FMT as an investigational drug, which imparts overly restrictive regulations that are impossible to apply to FMT in the same manner as conventional drugs. Reclassification of FMT to a human cell, tissue, and cellular and tissue-based product could potentially expand access to this important treatment while maintaining rigorous safety standards.

Fecal microbiota transplantation (FMT) is the transfer of stool from a healthy donor to provide "good bacteria" as a therapeutic agent and has emerged as a highly effective treatment for *Clostridium difficile* infections (CDIs). A recently published systematic review on the use of FMT to treat CDI showed that across all studies, 85% of patients with recurrent CDI treated with FMT achieved the resolution of symptoms [1]. FMT avoids problems associated with antibiotic use, including high cost, low efficacy, and the potential for recurrence and resistance. Notwithstanding the exceptional results among patients receiving FMT, the United States Food and Drug Administration (FDA) has legitimate concerns about the efficacy and safety profile of this treatment, particularly its long-term effects, and classifies FMT as an investigational drug. The encumbering regulations that accompany the investigational drug classification are impractical for applying to FMT in the same manner as conventional drugs. Reclassifying FMT to a human cell, tissue, and cellular and tissue-based product (HCT/P) could potentially allow greater numbers of patients to benefit from this effective treatment, while still maintaining the rigorous safety standards required for any human tissue intended for transplantation.

1. *Clostridium difficile*

CDI is the most frequent cause of hospital-acquired infectious diarrhea in developed countries [2] and accounts for 20–30% of all cases of antibiotic-associated diarrhea [3]. The hospitalization rate for CDI in the United States more than doubled from 2001 to 2011 [4], resulting in an estimated 453,000 incident CDIs and 29,300 deaths in 2011 [5].

CDI also creates significant financial costs. The cost of CDI treatment ranges from $3006 [6] to as high as $15,397 per patient [7]. The nationwide financial burden due to *C. difficile* is approximately $4.8 billion for acute care facilities alone [8].

The gut microbiota, the vast community of microorganisms in the gastrointestinal tract, protects the body from invading pathogens by competing for resources. *C. difficile* is an opportunistic pathogen that has become a serious problem in health care settings and is most commonly associated with hospitalized patients receiving antibiotic therapies. The antibiotics these patients receive can destroy the helpful bacteria and perturb the gut microbiota,

☆ Article summary: Fecal microbiota transplantation (FMT) has emerged as a highly effective treatment of *Clostridium difficile* infection and reclassification of FMT from investigational drug to human tissue may facilitate better access to this important treatment, while maintaining rigorous safety standards.

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http://dx.doi.org/10.1016/j.conctc.2015.11.001

thereby allowing *C. difficile* to flourish. CDI can also damage the colon and potentially allow bacteria to leak into the bloodstream, resulting in septicemia.

Antibiotic use may cause CDI, and, ironically, antibiotics are used to treat the infection. The most effective antibacterial treatment for CDI, vancomycin, is on the World Health Organization's List of Essential Medicines and is also used to treat a variety of infections, including potentially deadly methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

A key issue with vancomycin use for CDI treatment is the high rate of recurrence following the initial treatment. In one double blind, non-inferiority, randomized, controlled trial (RCT), the recurrence rate in patients treated with vancomycin for the initial CDI was 26.9% [9]. Recurrent CDI has recently become more common due (in part) to a new, hyper-virulent strain that is less responsive to traditional antibiotic treatments. Recurrent CDI is also associated with a significantly increased risk of death compared with that in CDI patients who do not develop recurrence [10,11].

2. Clinical efficacy of FMT

A systematic review designed to assess the efficacy, comparative effectiveness, and adverse effects of FMT for CDI treatment revealed that, across all studies for recurrent CDI, symptom resolution was observed in 85% of patients [1]. This review identified two randomized, controlled trials (RCTs) and 28 case-series studies regarding the efficacy of FMT for recurrent CDI, refractory CDI, or an initial episode of CDI. Most studies involved recurrent CDIs. In one RCT, 43 patients were randomly assigned to receive FMT, vancomycin, or vancomycin and bowel lavage. 81% of FMT patients achieved resolution of symptoms within three months compared with only 31% of patients who received vancomycin and 23% of patients who received vancomycin and bowel lavage [12]. The interim results of this trial demonstrated that FMT was significantly superior to standard antibacterial therapy. The results were so profound that the trial was terminated early in accordance with the Haybittle–Peto rule, which specifies a p-value (often $p < 0.001$) for stopping the trial early [13,14]. Overall, in the two RCTs, 75% of patients receiving FMT experienced the resolution of symptoms with no additional recurrence.

Interest in FMT is increasing, and the United States National Institutes of Health lists three active clinical trials investigating the use of FMT to treat CDI [15–17]. More than 40 additional trials are recruiting patients.

3. Classification and regulation of FMT

In 2012, the FDA classified FMT as an investigational drug. This classification requires an Investigational New Drug (IND) application for use in humans. Assembling a single IND application can take months or even years, and this time frame is unacceptable for patients requiring treatment for CDI. Due to considerable opposition from clinicians, in July 2013, the FDA issued a statement and declared a temporary enforcement of discretion when FMT is used clinically to treat CDI. Thus, for CDI patients, physicians may proceed with FMT without navigating the time-consuming process of filing an IND. However, there is no guarantee that this guideline will remain in place indefinitely.

Despite the remarkable results among patients receiving FMT, the FDA remains concerned about the efficacy and safety profile of this treatment, especially regarding the long-term effects. The potential challenges for defining FMT are related to the active ingredient, potency, stability, and manufacturing process. These concerns are legitimate, and although these issues are valid for an investigational drug, they should not impede the broad acceptance and use of FMT.

The human stool used for FMT is a highly variable mixture of inorganic and organic matter that inherently differs from a conventional drug in the sense that everyone naturally produces it. The current classification of FMT as an investigational drug imparts overly restrictive regulations, which are impossible to apply to FMT in the same manner as conventional drugs since it does not originate from pharmaceutical factories, nor is it created in a laboratory [18]. If the FDA reclassified FMT as a human cell, tissue, and cellular and tissue-based product (HCT/P), then FMT would be regulated under Title 21, Part 1270 and 1271 of the Code of Federal Regulations regarding human tissue intended for transplantation. FMT would then be regulated as other non-vascularized human tissue, such as bone, skin, corneas, and ligaments.

The HCT/P classification excludes products excreted from the body. However, there is a precedent for the FDA to make exceptions to this rule because the FDA classifies semen as human tissue. A similar exception might be made for FMT. Reclassifying FMT as an HCT/P could potentially expand access to care and alleviate restrictions on research while concurrently ensuring safety through the same mandatory screening of samples and recordkeeping required for any human tissue intended for transplantation.

Because FMT has a high cure rate in multiple trials with few serious adverse events [1,12,19,20], the timely reclassification of FMT to an HCT/P would most likely cause increased use of FMT and less antibiotic use.

Antibiotic resistance is a major hazard to public health and threatens the advancement of modern medicine [21]. FMT is proving to be more effective for treating CDI than traditional antibacterial therapy, and FMT reduces the risk of valuable antibiotics causing resistance. Therefore, the increased use of FMT would be mutually beneficial from both a patient and public health perspective. The awareness of FMT among the general public is increasing. However, the responsibility for increasing the use of FMT rests with medical practitioners, regulatory bodies, and the wider public health community. We argue that the public health would be served by better access to this important treatment when physicians deem it to be indicated, and the reclassification of FMT to an HCT/P is a potential avenue to increase this access.

Acknowledgments

We thank Melinda M. Pettigrew for her helpful comments. The authors received no external financial support for the writing of this manuscript.

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