CORRESPONDENCE

Fecal Microbiota Transplantation for Primary *Clostridium difficile* Infection

TO THE EDITOR: *Clostridium difficile* infection is a major health problem.[1] Antibiotic treatment is associated with a considerable rate of recurrence of infection and is related to the emergence of antibiotic-resistant bacteria. Recently, fecal microbiota transplantation has been shown to be effective in the treatment of recurrent *C. difficile* infection.[2] We undertook a proof-of-concept trial (ClinicalTrials.gov number, NCT02301000) to evaluate the use of fecal microbiota transplantation as treatment for primary *C. difficile* infection.

The trial began on November 25, 2014, and the first patient underwent randomization on February 22, 2015. From February 2015 through November 2017, at six hospitals in Norway, we randomly assigned 21 adult patients with acute *C. difficile* infection (≥3 loose stools per day and a positive *C. difficile* stool test) who had not had previous *C. difficile* infection to recommended treatment in Norway[3] (oral metronidazole at a dose of 400 mg three times a day for 10 days) or fecal microbiota transplantation (one 60-ml enema of anaerobically cultivated human intestinal microbiota) (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).[4,5] Achim Biotherapeutics, which provided the fecal microbiota suspension free of charge to the investigators for the purpose of the trial, had no role in the design, conduct, or analyses of the trial. The protocol, available at NEJM.org, was approved by the institutional review board, and all patients provided written informed consent.

The primary end point was clinical cure (firm stool consistency or ≤3 bowel movements per day) with no evidence of recurrence of *C. difficile* infection when the patient was evaluated at day 70 by an assessor who was unaware of the treatment assignment. Secondary end points were evaluations 4 and 35 days after the initiation of treatment and adverse events. Patients in whom clini-

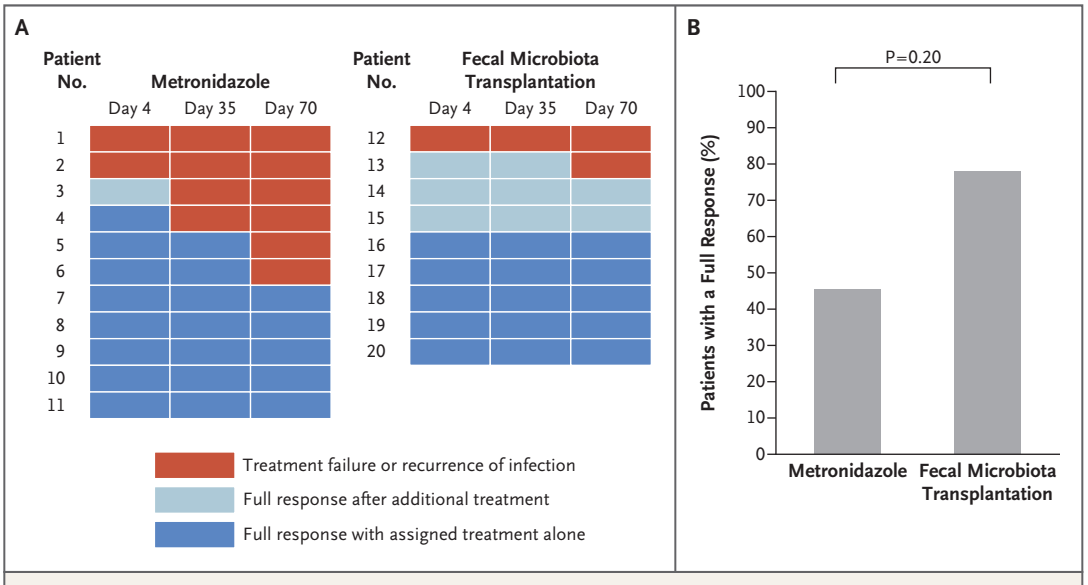

Figure 1. Results of Fecal Microbiota Transplantation versus Antibiotic Therapy with Metronidazole for Primary *Clostridium difficile* Infection.

Panel A shows the results at the evaluation of patients at 4, 35, and 70 days after the start of treatment. Panel B shows the overall response to treatment (full primary or secondary response after 70 days).

cal cure was achieved after initial treatment and who had no recurrence of infection were defined as having a full primary response. Patients who received additional treatment to achieve clinical cure, but who did not have recurrence of infection during the follow-up period, were defined as having a full secondary response. Full details of the trial are provided in the protocol and the statistical analysis plan, available at NEJM.org.

One patient was excluded because of a norovirus infection that was diagnosed the day after randomization. Of 20 eligible patients, 9 were randomly assigned to fecal microbiota transplantation and 11 were assigned to metronidazole. A full primary response was observed in 5 patients (56%; 95% confidence interval [CI], 21 to 86) in the transplantation group and in 5 in the metronidazole group (45%; 95% CI, 17 to 77) (exact P=1.00) (Fig. 1A).

Three of the four remaining patients in the transplantation group received antibiotics by day 4 after the initiation of treatment; two of them had a full secondary response. In the metronidazole group, of the remaining six patients, none had a full secondary response, either because of refractory or recurrent infection. Thus, the overall response to treatment (full primary or secondary response) was achieved in seven patients in the transplantation group (78%; 95% CI, 40 to 97), as compared with five in the metronidazole group (45%; 95% CI, 17 to 77) (P=0.20) (Fig. 1B). No serious treatment-related adverse events were observed in either group. Details on the treatment course of individual patients are provided in the Supplementary Appendix.

This was a small trial, but the results suggest that fecal microbiota transplantation may be an alternative to antibiotic therapy in primary *C. difficile* infection. A phase 3 trial to assess fecal microbiota transplantation as primary treatment for *C. difficile* infection is under way.

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