Fecal Microbiota Transplants May Aid Melanoma Immunotherapy Resistance

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—Christopher H. Woelk, PhD, and Alexandra Snyder, MD

According to 2 recent small phase 1 trials appearing in Science (2021;371:595-602. doi:10.1126/science.abb3363; 2021;371:602-609. doi:10.1126/science.abb5920), FMT may aid in reprogramming the human gut microbiome in patients with advanced melanoma. This may result in counteracting resistance to anti–PD-1 immunotherapy.

Several observational studies suggested an association between the gut microbiome of patients with metastatic melanoma and their responses to immune checkpoint inhibitor (CPI) therapies. Although it had also been shown that gut microbiota could influence the response of tumors to anti–PD-1 immunotherapy in preclinical mouse models, FMT had not previously been studied in clinical trials of human patients whose melanoma had persisted or progressed after anti–PD-1 immunotherapy.

One of the studies included 7 FMT donors and 15 recipients from the Department of Medicine at the University of Pittsburgh Hillman Medical Center (UPMC) in Pittsburgh, Pennsylvania, and the National Institutes of Health Clinical Center in Bethesda, Maryland. The second trial included 2 FMT donors and 10 recipients from the Ella Lemberbaum Institute for Immunology and Oncology at Sheba Medical Center in Tel-HaShomer, Israel. All FMT donors were patients with metastatic melanoma who had responded to anti–PD-1 immunotherapy. Both of the Israeli donors had a complete response (CR), whereas the Pittsburgh donors included 4 with a CR and 3 with a partial response (PR); the researchers hypothesized that their gut microbiomes had been a factor in these favorable outcomes and, therefore, might be of benefit to recipients who had been resistant to similar treatments.

The FMT protocol in both studies included an initial native microbiota depletion regimen, which consisted of vancomycin and neomycin. Patients then underwent FMT via colonoscopy and oral stool capsules, which were followed by re-induction of nivolumab anti–PD-1 therapy (in the Israeli study), or FMT via colonoscopy only, which was followed by pembrolizumab (in the Pittsburgh study).

Study Results
The outcomes of the 15 FMT recipients in the Pittsburgh study included 3 recipients with a PR and 3 with stable disease. Similar results were found for the 10 FMT recipients in the Israeli study: 1 CR and 2 PRs. Both research teams concluded that their findings suggest that FMT is safe and that altering the mix of bacteria in the gut microbiome can enhance the efficacy of immunotherapy in a subset of patients.

According to University of Pittsburgh senior study author Hassane M. Zarour, MD, professor of medicine, immunology, and dermatology, co-leader of the melanoma program at the Department of Medicine and UPMC Hillman Cancer Center, and James W. and Frances G. McGlothlin Chair in Melanoma Immunotherapy Research at the University of Pittsburgh, this research provides “proof of principle in patients with melanoma that demonstrates that we can manipulate the microbiome to augment and improve immunotherapy effectiveness by reprogramming the tumor microenvironment and overcoming resistance to anti–PD-1 in advanced melanoma.”
Dr. Zarour and his team also found that some PD-1–refractory patients may not respond to FMT for reasons that may include an inability to respond to the tumor, regardless of the microbiota composition, because of the patient’s immune-deficient status or possibly because of the lack of tumor immunogenicity. These researchers further wrote that there might also be an absence of bacterial taxa needed for anti-PD-1 therapy effectiveness in the FMT preparations, or there might be “failure of the FMT to successfully implant into the recipient and induce perturbations of host microbiota favoring anti-PD-1.”

In the Israeli study, the researchers observed clinical responses in 3 patients, including 2 PRs and 1 CR. In addition to observing clinical antitumor responses, both teams conducted a wide variety of molecular tests supporting the hypothesis that FMT altered the gut microbiome of some patients, which influenced the composition of their gut-associated immune cells, and the composition of their tumor-infiltrating immune cells.

“Notably, treatment with FMT was associated with favorable changes in immune cell infiltrates and gene expression profiles in both the gut lamina propria and the tumor microenvironment,” wrote lead investigator Erez Baruch, MD, PhD, who is currently a resident in internal medicine, physician–scientist pathway at UTHealth Houston, Texas.

Study Relevance

In a commentary accompanying both studies, Christopher H. Woelk, PhD, head of systems biology at Merck & Co’s Exploratory Science Center in Cambridge, Massachusetts, and Alexandra Snyder, MD, head of the translational oncology and diagnostics leadership team and global clinical development at Merck & Co in Rahway, New Jersey, agreed that there is a possible therapeutic effect of FMT in CPI-treated patients according to these studies. "However, several clinical, regulatory, and scientific questions need to be addressed for this approach to become an approved treatment. Also, larger studies in a defined post-CPI population are needed to show FMT efficacy," they wrote.

Dr. Baruch cautions, “At the moment, due to its complexity and associated risks if done improperly, microbiota modulation should remain in the highly monitored environment of clinical trials.”

Dr. Zarour from the University of Pittsburgh study agrees. He says that he is frequently asked if he thought that the results from this small group of patients would hold true with a larger group of patients. “I tell them we don’t know, and finding funding for these trials is difficult. This is just a proof of principle, and we don’t want to overstate the data since only 6 out of 15 patients had a favorable outcome. We believe further investigations are needed to better identify microbial, circulating, and intra-tumoral biomarkers in order to select patients most likely to benefit from microbiome-based therapy of melanoma.”

Dr. Baruch also points out how previous observational studies comparing gut microbiota of immunotherapy responders and nonresponders led to these 2 clinical trials. “This study was an example of how profiling the differences between responders and non-responders to a specific therapy can lead to the development of new therapies in only a few years.”

In their editorial, Dr. Woelk and Dr. Snyder also state, “Future work is needed to better understand which response profiles for sourcing donor FMT, engraftment procedures, and recipient phenotypes are required for successful CPI-FMT combination therapy.”

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