Editorial

One man's trash-another man's treasure: fecal transplantation

Nancy Gupta[1], **Stephen B. Hanauer**[2]

[1]Digestive Health Center, University of Iowa Hospitals and Clinics, Iowa City, IA, USA; [2]Digestive Health Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Correspondence to: Nancy Gupta. Department of Gastroenterology, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, USA. Email: drnancygupta87@gmail.com.

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Discovery of immune checkpoint inhibitors has revolutionized the field of oncology. Immune checkpoints play a key role in maintaining immune homeostasis and preventing autoimmunity. Under normal situation, immune responses are regulated by a balance between co-stimulatory and inhibitory signals referred to as "immune checkpoints". Activated T cells express multiple co-inhibitory receptors such as lymphocyte-activation gene 3 (*LAG-3*), programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that are primary mediators of immune effector responses to self-proteins, chronic infections and tumor antigens. In tumors these immune checkpoints allow the tumor cells to dodge anti-tumor response (1). Checkpoint inhibitors (CPI) block these immune checkpoints allowing the immune system to attack tumor cells (2). Although the immune system has the inherent ability to distinguish self from non-self and thus typically mount an attack on the non-self-cancer cells; over-activation of the immune response can lead to serious adverse events collectively called immune-related adverse events (irAEs) (3). While activation of the immune system and development of irAEs has been associated with better outcomes for underlying cancer (4), the associated side effects increase morbidity and mortality in addition to having a negative impact on patient's quality of life. irAEs associated with CPI therapy can have delayed manifestation and present after the CPI have been discontinued (5).

The gastrointestinal system is the most common organ system affected by irAEs and gastrointestinal inflammation attributed to CPI range from mild diarrhea (27%) to colitis or severe enterocolitis (12%) leading to intractable diarrhea, bleeding, perforation and even death (1%) (6). While the intestinal microbiome maintains the integrity of intestinal mucosal epithelium and modulates gut immunological responses (7), exposure to immune CPI also alters the gut microbial flora.

As with other colitis, management of CPI-associated colitis depends on disease severity. Management options include oral rehydration, anti-motility agents in mild colitis. In moderate to severe cases steroids, immunosuppressants such as TNF inhibitors, tacrolimus or mycophenolate have been utilized analogous to the treatment of inflammatory bowel diseases (IBDs) (8). Rarely, colectomy has been required for severe colitis refractory to steroids, however, requisite surgery is challenging in context of the poor prognosis for metastatic disease. Further uncertainties regarding the impact of additional immune suppression in patients with metastatic disease relate to potential impact on the evolution of the primary tumor (9).

Hence, exploring non-systemic therapies for irAEs that act at the gut mucosal level and preclude additional immune suppression would be desirable. Fecal transplantations have had the most documented impact on recurrent C. difficile infections (>90% cure rate) (10) and are being studied in patients with idiopathic IBDs (10). In their paper, Wang *et al.* have evaluated fecal transplants as an approach to patients with irAE refractory colitis (11).

Thus far, experience with fecal transplants in patients with ulcerative colitis suggests that the response rates of fecal transplants are inversely proportional to underlying disease severity (12). Perhaps counterintuitively, Wang *et al.* have shown the success of fecal transplant in patients

with "refractory" colitis. Whether this is anecdotal or more generalizable remains to be proven, but, if demonstrated to be safe and effective, there may be an increasing role for fecal transplantation in check point inhibitor colitis (and possibly for other irAEs) (13).

In both IBD and CPI colitis the gut microbiome has been found to be less diverse than in healthy individuals. In the paper by Wang *et al.*, fecal microbiome analysis of the patients after fecal transplantation showed that there was an initial increase in the number of bacterial species that eventually reduced over time although there was an increase in the population of *Bacteroides* species that have been considered "gut protective" (14). Whether the increase in bacterial diversity as a whole, or engraftment with specific phyla such as *Bacteroides* abrogates inflammation in active colitis remains to be determined.

In patients treated with fecal transplants for *Clostridium* difficile and ulcerative colitis, repeated application of transplanted microbiome is often necessary (15). In the report by Wang *et al.*, some patients also required a second administration of donor feces to achieve a complete response (11). Further studies of pre-specified donor flora along with optimal dosing and dosing intervals will be required for the fecal transplantation within the spectrum of CPI-induced colitis along with long-term follow-up of treated patients.

Further understanding of the role of the microbiome in inducing CPI colitis and the potential of pre-CPI "probiotics" to prevent irAEs are needed. Besides, means to prospectively assess the gut microbiome at intervals following treatment initiation with CPI might help identify the transition point at which the fecal microbial environment changes to a potentially pathogenic pattern.

Similar to the potential for fecal transplants to treat idiopathic ulcerative colitis exploration of this novel approach to the treatment of refractory CPI-colitis is in its infancy. Ultimately, the "gross" transplantation of stool from healthy donors will be replaced by more "targeted" microbes or communities of microbes that could be commercially produced and validated as preventative or therapeutic. In the meantime, further evaluation and understanding of predisposing and therapeutic microbes in immune-mediated inflammatory disorders, including CPI-colitis is an exciting, challenging and already expanding field of study.

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Footnote

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