Fecal transplantation improved patients' reported outcome after immune checkpoint inhibitor colitis

Yinghong Wang[1], Malek Shatila[1], Krishnavathana Varatharajalu[1], Shu-En Shen[2], Mary Herrera[2], Elizabeth Gonzalez,[2] Xin S. Wang[2], Anusha Thomas[1], Zhi-Dong Jiang[4], Herbert DuPont[5]

[1] Department of Gastroenterology Hepatology and Nutrition, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, 77030; [2] Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, 77030; [3]UTHealth School of Public Health and Kelsey Research Foundation, Houston, TX, USA, 77030; [4]UTHealth School of Public Health, Houston, TX, USA, 77030

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Introduction

Immune-mediated colitis (IMC) is a potential adverse drug effect following treatment with immune checkpoint inhibitors (ICIs) and poses a significant obstacle to effective cancer management. Currently, the first-line treatment for cases grade 2 and above (as measured by CTCAE) is corticosteroids +/- infliximab or vedolizumab. There are a few alternatives for refractory cases such as tofacitinib and ustekinumab, but no large-scale studies have supported their use. Fecal microbiota transplantation (FMT) on the other hand has received increasing attention as a potential therapeutic option for these cases. Our previous case series with 15 patients showed a success rate of over 75% for FMT in treating refractory cases. FMT is an appealing treatment modality primarily as a means of avoiding prolonged immunosuppression in these patients, mitigating the risk for infection and steroid-related complications. In this study, we further expanded our sample size for the assessment of the safety and efficacy of FMT as well as patients' reported outcome in the management of IMC cases refractory to standard treatments.

Methods

This study is a review of treatment outcomes in patients enrolled in an ongoing clinical trial (NCT03819296) on the use of FMT for refractory IMC. Only patients who completed their study follow-up thus far were included. Clinical information including demographics, disease course, and treatment outcomes were obtained via chart review and clinical assessment, and patient-reported outcomes (PRO) were obtained via the validated MD Anderson Symptom Inventory.

Results

Thirty-seven patients were included in our study with a median age of 59 (51-70) years and a male predominance (75%). Genitourinary cancers were the most common malignancy (35.1%) followed by melanoma (27.0%), and the majority were stage IV (89.1%). Cancer treatment included either PD-1/L1 inhibition (51.3%) or a combination of PD-1/L1 and CTLA-4 inhibitors (43.2%); only 2 patients (5.4%) received anti-CTLA-4 agents alone. All patients except one (97.3%) stopped ICI because of colitis after a median of 7 (3-12) doses. On PRO analysis, we observed a favorable trend of significant patient-reported symptom reduction on diarrhea during the 12 weeks after FMT, along with improved daily physical functioning on working (Figure 1).

Figure 1. Trends in severity of most common patient-reported symptoms up to twelve weeks after FMT.

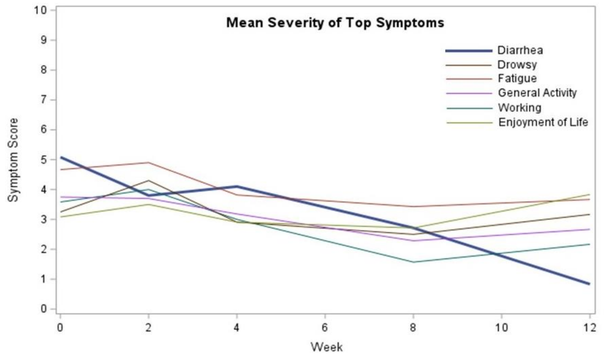

Table 2 Characteristics and outcome of immune-mediated colitis (n = 37)

Characteristic before FMT	No. (%) (n=37)
Concurrent CDI	9(24.3%)
Median time from ICI to IMC – days (IQR)	137 (44-255)
Highest grade of diarrhea of initial IMC onset, 3-4 – no. (%)	34 (91.9%)
Highest grade of colitis of initial IMC onset, 3-4 – no. (%)	33 (89.2%)
Initial endoscopic findings – no (%), n=36	
Ulcers	18 (48.6%)
Non-ulcer inflammation	12 (32.4%)
Normal	6 (16.2%)
Initial histology findings – no (%), n=35	
Active inflammation	5 (14.3%)
Chronic active inflammation	27 (77.1%)
Hospitalizations – no. (%)	29 (78.3%)
Median duration of hospitalization – days (IQR)	8 (5-13)
Treatment of GI adverse events – no. (%)	
Steroid	36 (97.3%)
Infliximab/vedolizumab added	33 (89.1%)
Overall median duration of steroid treatment – days (IQR)	85 (44-120)

FMT characteristics and outcome	No. (%) (n=37)
Median time from initial IMC to FMT– days (IQR)	121 (75-226)
Symptom improvement after FMT – no (%)	31 (83.7%)
Symptom improvement after FMT (no concurrent CDI, n=28) – no (%)	24 (85.7%)
Median time from FMT to symptom improvement– days (IQR)	5 (2-10)
FMT-related complications within 7 days –no (%)	6(16.2%)
FMT-related complications within 30 days –no (%)	2(5.4%)
Cancer status at the time of FMT –no (%)	
Remission or stable disease	24 (64.8%)
Required immunosuppressants for recurrent or refractory colitis after FMT – no (%)	4 (10.8%)
Resumed cancer treatment after FMT – no (%)	11 (29.7%)
Colitis status at the end of the study period	
Clinical remission – no (%)	35 (94.6%)
Persistent symptoms – no (%)	2 (5.4%)
Cancer status at last follow-up –no (%)	
Remission or stable disease	20 (54%)
Mortality– no. (%)	17 (45.9%)

Discussion

This is the largest study to date supporting the effectiveness of FMT in managing immune-mediated diarrhea and colitis refractory to standard-of-care treatment of steroids and selective immunosuppressive therapy and improving patients' reported outcome. Our results show that this is a safe and promising therapeutic option with a low complication rate. The majority of patients who underwent FMT in this study had symptom improvement, and a very small proportion required additional treatments after FMT. These findings demonstrate the utility of FMT in treating refractory IMC and potentially supports a lower threshold for resorting to this procedure in difficult to manage cases. This is especially important as it provides another avenue for physicians to treat these cases that avoids the long-term immunosuppression these patients usually receive and the corresponding complications. Future research is still needed before FMT becomes a commonplace treatment modality; in particular, prospective studies are needed to validate its use. Moreover, the role of the gut microbiome in IMC disease course, cancer outcomes, and efficacy of ICI therapy has yet to be fully elucidated and warrants further study.

Conclusions

FMT may serve as a potential treatment option in IMC refractory to standard treatment to avoid long-term steroid dependency and immunosuppression. It is effective to maintain IMC remission with a low complication rate. The role of the gut microbiome in cancer and the implications for FMT still needs further clarification.

CONTACT

Yinghong Wang MD PhD
Department of Gastroenterology, Hepatology and Nutrition, Unit 1466, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030
Email: ywang59@mdanderson.org
Phone: 713-794-5398