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EDITORIAL

Dual-targeted treatment for inflammatory bowel disease: Whether fecal microbiota transplantation can be an important part of it

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Abstract

Inflammatory bowel disease (IBD) is a chronic gastrointestinal inflammatory disease. With the emergence of biologics and other therapeutic methods, two biologics or one biologic combined with a novel small-molecule drug has been proposed in recent years to treat IBD. Although treatment strategies for IBD are being optimized, their efficacy and risks still warrant further consideration. This editorial explores the current risks associated with dual-targeted treatment for IBD and the great potential that fecal microbiota transplantation (FMT) may have for use in combination therapy for IBD. We are focused on addressing refractory IBD or biologically resistant IBD based on currently available dual-targeted treatment by incorporating FMT as part of this dual-targeted treatment. In this new therapy regimen, FMT represents a promising combination therapy.

Key Words: Gut microbiota; Inflammatory bowel disease; Fecal microbiota transplantation; Dual-targeted treatment; Combination treatment

Core Tip: The combination of biologic agents or the combination of a biologic agent and a novel small-molecule drug for treating inflammatory bowel disease (IBD) carries certain risks, and some patients are resistant to these drugs. The regulation of the gut microbiota has become a potential treatment for IBD, and the inclusion of fecal bacteria transplantation in dual-targeted treatments for IBD holds great promise.

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INTRODUCTION

Despite the great progress that has been made in the development of dual-targeted treatments for inflammatory bowel disease (IBD), many patients are resistant to biologics or experience adverse reactions, and the therapeutic effects are not ideal. Lowell *et al*[1] also highlighted the lack of high quality and good safety data about dual-biologic therapies. Moreover, there may be risks of infection, risks of malignant tumor development and other risks associated with biologic therapy. These problems associated with dual-targeted treatment are worthy of in-depth consideration, and efforts to resolve these problems would be worthwhile.

There are many microbes in the human intestine that affect the body's physiology and metabolism, as well as health and disease. Therefore, maintaining the homeostasis of the gut microbiota is also considered to be the key to maintaining health. The pathogenic factors of IBD are complex, and numerous studies have shown that the occurrence and progression of IBD are related to changes in the gut microbiota, these changes have become a potential target for treating IBD. Fecal microbiota transplantation (FMT) involves the transfer of the gut microbiota from a healthy donor, which introduces an intact, stable microbiota into the gut of a recipient to repair or replace disrupted natural microbiome of the recipient. The purpose of this editorial is to discuss new ways to address refractory IBD or biologically resistant IBD by including FMT in the current IBD combination therapy regimen for treating IBD.

COMBINATION THERAPY FOR IBD

Current status of combination therapy for IBD

There have been significant advances in the treatment of IBD in recent years. For some patients with severe or refractory IBD, a combination of two biologics can also be used. At present, biologic dual combination therapy mainly consists of tumour necrosis factor (TNF)-α antagonist and vedolizumab, ustekinumab and vedolizumab, TNF-α inhibitor and vedolizumab, among these, the most common combination is a TNF-α inhibitor and vedolizumab, followed by ustekinumab and vedolizumab. The combination of biologics and small molecule drugs is mainly involves tofacitinib combined with a biologic (including vedolizumab, infliximab, and ustekinumab).

When one biologic agent is used alone, IBD treatment can achieve a maximum clinical response rate of approximately 40%–60%[2]. A recent review of 30 studies by Ahmed *et al*[3] reported 288 trials of dual biologic or small molecule therapies in 279 patients. This study focused on the most common biologic dual biologic regimens, namely, an anti-TNF agent and vedolizumab (48%). Studies have shown a combined clinical response rate of 59% (95%CI: 0.42–0.74) and an endoscopic response rate of 34% (95%CI: 0.23–0.46)[3]. Gold and Steinlauf[4] summarized data from 209 published studies on dual-targeted treatment, including retrospective studies, case series, and case reports. This review suggested that dual-targeted treatment may be effective in inducing remission in patients with refractory intestinal symptoms and/or parenteral manifestations. The authors reported an effectiveness range of 67% to 80%. No serious adverse events were described[5]. Mas and Calvo[5] summarized the safety and reliability of various studies and biological combinations. The review revealed that the clinical response rate, clinical response rate, endoscopic response rate, and endoscopic response rate of patients treated with the TNF-α antagonist and vedolizumab were 50%, 29%, 58%, and 25%, respectively. For ustekinumab and vedolizumab, these data were 80%, 57%, 76% and 25%, respectively. For TNF-α antagonist and ustekinumab, these data were 44%, 57%, 33% and 33%, respectively. The above studies and data show that the efficacy of dual-targeted treatment is worthy of affirmation for patients with very severe IBD. But at the same time, dual-targeted treatment may have more risks[5].

POSSIBLE RISKS OF DUAL-TARGETED TREATMENT

Infection risk

Biologics achieve therapeutic effects mainly by targeted intervention in different stages of the immune response. However, due to the poor nutritional status and immune function of patients with IBD along with the immune suppression caused by related drugs, the ability of these patients to resist pathogen invasion is weakened, significantly increasing the risk of opportunistic infections[6]. Sheriff *et al*[6] studied 27300 cases of opportunistic infections (OI) in Crohn's disease (CD) patients and 24690 cases of OI in UC patients and reported that the prevalence of OI in CD patients, UC patients, and non-IBD controls was 17.8%, 19.2%, and 7%, respectively. Compared with non-IBD controls, OIs were more commonly found in CD [pregnancy rate (PR): 2.54; 95%CI: 2.51-2.57] and UC (PR: 2.74; 95%CI: 2.71-2.77) patients. Overall, viral infections were numerically more common in patients with CD and UC than in IBD-free controls, while bacterial infections had the highest risk ratio[6].

Privitera *et al*[7] reported the largest cohort of patients with IBD receiving dual-targeted treatment, including 113 patients. Adverse events were reported in 13%–30% of patients, with infections being the most common. Another study revealed that the risk of opportunistic infection with either immunosuppressant was 3.247 (95%CI: 1.128-9.341), whereas the risk of opportunistic infection with any two immunosuppressants was 6.457 (95%CI: 1.726-24.152); moreover, patients with IBD who used both immunosuppressants in combination had a significantly greater risk of concurrent opportunistic infections than those who used either immunosuppressant alone[8]. Bacterial infections were more common in patients with IBD than in non-IBD patients. Among these infections, *Clostridium difficile* was the most prevalent opportunistic bacterial disease. Studies have shown that the prevalence of *Clostridium difficile* in patients with CD is significantly lower than that in patients with UC[6].

TNF-α plays a central role in granulomatous formation, and its inhibition can lead to the reactivation of granulomatous disease. Therefore, biologics may increase the risk of tuberculosis (TB) infection and cause reactivation of latent TB infection in patients with IBD receiving dual-targeted treatment, making routine screening for TB essential before TNF-α inhibitor application. It is also possible that hepatitis B can be reactivated by anti-TNF therapy. Reactivation of tuberculosis and hepatitis B in patients who are treated with these drugs has resulted in significant morbidity and mortality[9].

Malignant tumors

Among the risk factors for related malignancies, lymphoma is currently the focus of attention. The risk of lymphoma was greater in patients treated with either monotherapy or a combination of TNF-α inhibitors than in those who did not use these biologics. Nineteen percent of patients with lymphoma were exposed to thiopurine, 19% were exposed to TNF-α inhibitors, and 43% were exposed to combination therapy. Compared with treatment with TNF-α inhibitors alone, dual-targeted treatment is associated with a greater risk of lymphoma[10]. The identified high-risk tumors were not non-Hodgkin lymphoma, but Hodgkin lymphoma and T-cell lymphoma. Although T-cell lymphoma is very rare, it deserves special attention given its poor prognosis.

FMT AS PART OF DUAL-TARGETED TREATMENT FOR IBD: WHAT DO WE KNOW? WHAT DO WE EXPECT?

What do we know about the role of the gut microbiota in the development of resistance to targeted therapies in cancer patients

The gut microbiota can affect the efficacy of anticancer drugs: The gut microbiota can influence the response of patients to anticancer treatments by modulating the host immune system. Di Modica *et al*[11] discussed the influence of the gut microbiota on the efficacy of trastuzumab in the treatment of human epidermal growth factor receptor 2-positive breast cancer. Experiments in mice revealed that the tumor growth inhibition observed after trastuzumab treatment was more effective in mice transplanted with feces from conventional (NoA) animals (FMT-NoA) than in mice treated with donor feces from mice treated with vancomycin (FMT-vancomycin) with vancomycin (altered gut microbiota). Experimental studies have confirmed that after trastuzumab treatment, the gut microbiota changes the tumor immune microenvironment by regulating the recruitment of $CD4^+$ T cells and granzyme B positive cells to tumor cells, thus regulating the therapeutic effect of this drug[11]. Studies by Ma *et al*[12] have also shown that the gut microbiota can affect cell-based immunotherapy, and the bile acid metabolism that is mediated by the gut microbiota increases the number of chemokine ligand 1 natural killer T cells in the liver, playing an antitumor role in hepatocellular carcinoma. In addition, Zhang *et al*[13] showed that *Fusobacterium nucleatum* promoted the secretion of chemotherapy-induced senescence related secreting phenotypes by activating the DNA damage response pathway and promoted the progression and chemotherapy resistance of esophageal squamous cell carcinoma. Thus, the gut microbiota is expected to be a potential target for drug-resistant squamous cell cancers such as esophageal cancer.

The composition and diversity of the gut microbiota can influence the efficacy of anticancer therapy. Gopalakrishnan *et al*[14] demonstrated that in melanoma patients, the diversity and composition of the gut microbiota were positively correlated with the response to anti-programmed cell death protein-1 (PD-1) treatment. Therefore, the regulation of patients' gut microbiota by FMT (*e.g.*, transplantation of feces with high microbial diversity and abundance of Rumenococcaceae and Faecalibacterium) can increase systemic and antitumor immune responses by increasing antigen presentation and improving effector T-cell function in the peripheral and tumor microenvironments[14]. These findings highlight the therapeutic potential of applying FMT to regulate the gut microbiome in patients undergoing checkpoint blockade immunotherapy to treat tumors.

FMT is effective in patients with secondary failure of anticancer drugs: Anti-PD-1 therapy can provide long-term clinical benefits for patients with advanced melanoma. Davar *et al*[15] used FMT combined with anti-PD-1 therapy to treat anti-PD-1 refractory melanoma. The experimental results revealed that FMT and anti-PD-1 antibodies changed the gut microbiota. In addition, this approach reprogrammed the tumor microenvironment to overcome resistance to anti-PD-1 antibodies in the PD-1 advanced melanoma subgroup[15].

In the study by Lu *et al*[16], FMT was reported to further improve the response to immune checkpoint inhibitors (ICIs) by regulating the composition and diversity of the gut microbiota through FMT. Among patients with non-small cell lung cancer and renal cell carcinoma, those with greater bacterial diversity were more sensitive to anti-PD-1 therapy. Oral supplementation of Myxophilus after FMT in ICIs nonresponders can restore the anti-PD-1 therapeutic response[16].

What are our expectations about the role of the gut microbiota in dual-targeted treatment for IBD

The gut microbiota can affect the treatment effect of IBD: IBD is the result of a combination of environmental, microbial, immune and genetic factors[17], and its occurrence and progression are related to changes in some gut microbiota. Therefore, regulating the gut microbiota has emerged as a potential treatment for IBD. For some patients with refractory IBD or who have an adverse response to current treatments, FMT may be considered. Research suggests that FMT may be an effective and largely safe alternative treatment for patients with IBD. A study by Anderson *et al*[18] revealed that the use of FMT to treat active IBD resulted in a reduction in or complete remission of symptoms in 76% of patients, cessation of all IBD medications in 76% of patients, and "prolonged remission" of active disease in 63% of patients. The majority (86%) of patients who were previously refractory to IBD drugs or limited to subtherapeutic doses later responded to these drugs. Most articles reported no cases of recurrence or adverse events directly related to FMT.

FMT is equally effective in patients with secondary failure of biologics: A new development direction: At present, the main treatment options for IBD are traditional drug therapy and new biologic therapy, but a considerable proportion of patients still experience secondary loss of response or no response to therapy. Studies have shown that the incidence of primary nonresponse is approximately 6%-24%[19,20] and the incidence of secondary non-response nonresponse is approximately 30%-40%[21,22]. Moreover, IBD is characterized by repeated attacks and a prolonged course of disease. As such, the psychological and economic burdens of patients and their families increase accordingly. Therefore, development of treatment plans for patients for whom multiple biologics fail is a new problem worthy of attention and exploration.

Based on the immunostimulatory effect of the gut microbiota in cancer patients who are resistant to targeted therapy, it may also play an important role in the state of nonresponse to IBD biologics. Compared with dual-targeted treatment, FMT combined with biologics may be a more effective and safer way to control the gut microbiota. FMT increases the bacterial diversity of the recipient's gut microbiota, and combining FMT with biologics may help improve the therapeutic effect of IBD.

INTESTINAL MICROBIOTA COMBINED WITH IBD

Oral probiotics

Probiotics are beneficial microorganisms in the gut that have been widely used to treat various diseases. It has been proposed that genetically engineered probiotics can effectively deliver and continuously produce therapeutic drugs, regulate the intestinal microbiota, improve the richness of the intestinal microbiota, and thus relieve intestinal inflammation.

Fecal microbiota transplantatian

Treatment of IBD by FMT: Another effective way by which the gut microbiome contributes to the treatment of IBD *via* FMT. Unlike the concept of probiotics, FMT transfers the gut microbiota from a healthy donor to the patient with IBD, introducing an intact, stable microbiota into the recipient gut to repair or replace the disrupted natural microbiota. Restoring normal microbiome structure in IBD patients through FMT may be a promising approach.

FMT is a supplement to the effect of dual-target therapy: The use of biologics to treat IBD increases the risk of infection to some extent, whereas FMT treatment has a very low risk of infection. Multiple studies have shown an increased risk of TB in patients treated with biologics, and emerging experimental and epidemiological evidence highlights an important cross-dialogue between the gut microbiota and the lung, known as the "enteropulmonary axis"[23]. Therefore, FMT may have a regulatory effect on the risk of infection, such as tuberculosis, that may occur with biologic therapy.

In light of the possible risk of malignant tumors development after treatment with biological agents, a number of studies have shown that the composition of the microbiome is closely related to tumors, which can affect the occurrence, development and response of tumors to immunotherapy, providing new clinical insights. By transplanting a functional microbiota from the stool of healthy individuals, FMT has produced responses in patients who have not responded to ICIs treatment, thus making FMT a promising new method for treating tumors that is expected to improve the prognosis of patients with malignant tumors[24].

Therefore, FMT has an important complementary effect on the possible adverse risks of IBD dual-target therapy, which can improve the treatment, prognosis and economic problems of patients with IBD.

CONCLUSION

The immunostimulatory effect of the gut microbiota in cancer patients who are resistant to targeted therapy is significant. Based on this, we believe that the gut microbiota may also play an important role in the state of nonresponse to IBD biologics. FMT is the most direct way to change the composition of the gut microbiota. The combination of FMT and biologics offers new ideas for the treatment of refractory IBD, although further clinical studies are needed to confirm these findings. The combination of FMT and biologics is worthy of further exploration, and with the rapid development of the gut microbiota, this combination therapy regimen is likely to become a very promising therapeutic strategy in the near future.

FOOTNOTES

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