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Research Progress in the Combination of Traditional Chinese Medicine and Targeted Anti-Tumor Necrosis Factor Therapy for Ulcerative Colitis

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Abstract: ***Ulcerative colitis (UC) is a chronic inflammatory disease that currently has no cure, and its pathogenesis is still unclear. The latest drugs for the treatment of moderate to severe UC in Western medicine include biologics, such as anti-tumor necrosis factor-alpha (TNF-α) monoclonal antibodies. However, due to the stability, safety, and adverse reactions of these drugs, their clinical applications are somewhat restricted. Traditional Chinese medicine, with its flexible treatment methods and minimal toxic side effects, and its ability to maintain long-term remission, is increasingly favored by more patients. The combination of Chinese and Western medicine has become a trend in the treatment of UC. This article provides a review of the combination of traditional Chinese medicine and targeted anti-TNF-α therapy for UC, aiming to provide new insights into safe and effective UC treatment.***

Keywords: Traditional Chinese medicine, Targeted therapy, Anti-tumor necrosis factor, Ulcerative colitis.

1. Introduction

Ulcerative colitis (UC) is a nonspecific intestinal disease characterized by diffuse, continuous inflammatory changes in the mucosa of the colon and rectum. The primary lesions are located in the mucosa and submucosa [1]. In February 2018, UC was classified as a major difficult disease by three ministries (the National Administration of Traditional Chinese Medicine, the National Health Commission, and the Logistics Support Department of the Central Military Commission). In Western medicine, UC is categorized under inflammatory bowel disease (IBD), while in Traditional Chinese Medicine (TCM), it falls under the categories of "diarrhea" and "dysentery" [2,3]. Currently, there are approximately 90,000 to 100,000 new UC cases worldwide each year, with the incidence showing an increasing trend year by year [4,5].

2. Current Status of Western Medicine Diagnosis and Treatment of UC

The exact pathogenesis of UC remains unclear in Western medicine, but it is believed to result from the interaction of multiple factors, including environment, genetics, psychological factors, immune abnormalities, and infections [6]. The main symptoms include abdominal pain, diarrhea, and recurrent mucus and blood in the stool. In recent years, the incidence of UC has increased, accompanied by complicated complications and difficult recovery, placing a significant burden on patients and society [7]. Currently, UC diagnosis requires a comprehensive assessment based on clinical presentation, gastrointestinal endoscopy findings, and corresponding pathological and imaging tests. The main goals of treatment are to reduce inflammation, slow disease progression, decrease recurrence and surgery rates, and improve the patient's quality of life. Endoscopic mucosal healing (Mayo endoscopic score = 0, or UC endoscopic severity index ≤1) is the preferred long-term treatment goal [8]. Traditional treatment methods include aminosalicylates, corticosteroids, immunosuppressants, immunomodulators, and antibiotics. Patients who are unresponsive to medication often require surgical resection [9]. For patients with refractory moderate to severe UC, at least one of the conventional treatments may be ineffective or intolerable. The advent of biologic agents has alleviated the dilemma of having no available treatment options for these patients. Numerous randomized controlled trials have provided high-quality evidence supporting the use of tumor necrosis factor (TNF) inhibitors [10,11]. TNF-α monoclonal antibodies, as the cornerstone of targeted biologic therapies for UC, are currently the primary drugs for treating moderate to severe UC [12,13].

2.1 The Mechanism of TNF-α in UC

TNF-α is primarily produced by macrophages, monocytes, and granulocytes. In ulcerative colitis (UC), TNF-α exerts its effects locally in the intestinal mucosa through both autocrine and paracrine mechanisms. On the one hand, integrins are activated and expressed under the influence of TNF-α, leading to an increase in intracellular Ca2+ concentration, which triggers the release of platelet-activating factor. This promotes the aggregation of lymphocytes, platelets, and leukocytes on the intestinal mucosal endothelial cells, subsequently inducing nitric oxide synthase isoforms, resulting in the production of large amounts of nitric oxide, ultimately causing cell damage. On the other hand, the morphological structure and barrier function of intestinal epithelial cells are altered under the combined action of TNF-α and interferon-γ, increasing the permeability of the intestinal mucosa and blood vessel walls, disrupting the integrity of the intestinal mucosa, and ultimately leading to ulcer formation. Alternatively, TNF-α can reduce the release of thrombomodulin, promoting a hypercoagulable state in the body, which, based on the patient's underlying microvasculitis, leads to the formation of microthrombi and ultimately causes microcirculatory disorders in the intestinal tissue. Additionally, cytokine

release is accelerated under the action of TNF-α, thereby amplifying the inflammatory cascade in the intestinal tissue and ultimately contributing to the chronic inflammation characteristic of UC [14,15]. The anti-TNF drugs currently used in the treatment of UC include infliximab (IFX), adalimumab (ADA), and golimumab (Golimumab).

2.2 Anti-TNF-α Monoclonal Antibodies

IFX is a chimeric human-mouse monoclonal antibody that blocks inflammation by binding to both soluble and transmembrane TNF. It was first approved by the U.S. FDA for use in IBD patients in 1998, and it was approved in China in 2019 for the treatment of UC [16,17]. It is also recommended by the American College of Gastroenterology as a first-line treatment for acute severe UC due to its rapid onset of action and significant effects in inducing and maintaining remission, making it widely used in clinical practice. The standard regimen involves an initial dose of 5 mg/kg for induction (at weeks 0, 2, and 6), followed by maintenance therapy every 8 weeks. This regimen not only achieves a high clinical remission rate but also reduces the use of corticosteroids. Compared to a single induction regimen, a three-dose induction regimen further reduces the rate of surgery [18]. IFX is superior to ADA in terms of inducing response, but not in maintaining remission. No significant difference has been observed among various biologics in terms of induction of remission [19]. In terms of drug administration, although subcutaneous administration of IFX has superior pharmacokinetic properties compared to intravenous injection, both methods show similar rates of remission and safety in UC patients [20].

ADA is a fully humanized IgG monoclonal antibody with relatively low immunogenicity. It has the advantages of stable efficacy and ease of use, and has been clearly shown to be safe for inducing and maintaining remission in moderate-to-severe UC patients who are unresponsive or intolerant to IFX. However, its onset of action is slower than that of IFX. Currently, it is only approved for use in China for the treatment of Crohn's disease (CD) [21].

Gol is a fully human monoclonal antibody that was approved by the European Commission in 2013 for the treatment of refractory moderate-to-severe UC. Since then, it has also been approved for the treatment of inflammatory arthritis conditions such as rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Although its long-term tolerance is similar to other anti-TNF-α inhibitors, it has the potential advantage of less frequent dosing [22].

Although targeted inhibition of TNF-α provides significant relief for moderate-to-severe UC, improving fecal microbiota and intestinal mucosal microbiota, and significantly promoting the recovery of intestinal barrier function [23-25], as many as 30% of patients exhibit primary non-response after anti-TNF-α induction therapy, and approximately 13%-25% of patients develop secondary non-response over time [26-28]. Even with aggressive biologic therapy, the rate of colectomy remains between 8% and 38% [29].

3. TCM Understanding of UC

Traditional Chinese Medicine (TCM) views ulcerative colitis (UC) as belonging to categories such as "intestinal wind," "dysentery," "stagnation," "diarrhea," "intestinal collapse," "abdominal pain," "blood in stool," and "visceral toxins." Poor diet, exposure to external pathogens, and emotional disturbances are considered key triggers for the disease [30]. The primary location of the disease is in the large intestine, with the fundamental pathogenesis linked to spleen dysfunction and closely associated with imbalances in the liver, lungs, kidneys, and other organs. During the active phase, the disease is characterized by excess patterns, with the main pathogenic mechanisms being the intermingling of dampness, heat, and cold, qi stagnation, blood stasis, and toxin accumulation in the intestines. Common symptoms include abdominal pain before bowel movements, relief after passing stool, and blood in the stool. During the remission phase, deficiency becomes more prominent, with the main pathogenesis involving spleen deficiency, disrupted transport and transformation of fluids, and may also include features of yang deficiency, lung deficiency, kidney deficiency, and liver stagnation, resulting in chronic and unresolved symptoms [31]. According to expert consensus on TCM diagnosis and treatment, UC is primarily classified into several syndromes, including large intestine damp-heat, intense heat-toxicity, spleen and kidney yang deficiency, mixed cold and heat, spleen deficiency with dampness retention, liver stagnation with spleen deficiency, and yin and blood deficiency [32,33].

Professor Wu Yiling [34], based on the "meridian disease" theory, believes that "qi stagnation initially affects the channels, and prolonged stagnation injures the blood, eventually affecting the meridians." He emphasizes that the fundamental treatment should focus on unblocking the meridians. Professor Xie Sheng [35], based on the "pivot theory," holds that "spleen deficiency with excessive dampness" represents the manifestation of UC, while "lung qi stagnation and disharmony between liver and lung" is the core of the pathogenesis. Good therapeutic outcomes can be achieved by regulating the liver and lung to harmonize the spleen and stomach.

Additionally, external treatments in TCM, such as acupuncture, herbal enemas, acupoint applications, and acupoint embedding, are commonly used in clinical practice and have shown significant efficacy. The main advantages of traditional Chinese medicine in treating UC lie in its flexibility, minimal toxicity, and side effects, as well as its ability to maintain long-term remission and reduce relapse rates.

4. Current Research Status of Combined Traditional Chinese Medicine (TCM) and TNF-α Targeted Therapy in the Treatment of Ulcerative Colitis (UC)

The advent of TNF-α targeted therapy has enabled the healing of the intestinal mucosa in UC patients. However, long-term clinical outcomes have shown that targeting a single pathway is unlikely to achieve a cure. Additionally, TNF-α inhibitors have limitations in clinical use due to primary non-response, secondary loss of response, and potential risks such as cancer or tuberculosis. On the other hand, traditional Chinese

medicine (TCM) has shown significant therapeutic effects in UC, effectively controlling the progression of the disease and alleviating clinical symptoms. As a result, an increasing number of patients are seeking TCM-based treatments. Many researchers have begun exploring whether TCM interventions could address the shortcomings of TNF-α targeted therapy.

Wang He observed that a combination of curcumin enema and infliximab (IFX) for the treatment of refractory ulcerative colitis (RUC) resulted in better outcomes than IFX alone, including lower levels of interleukin-1 (IL-1), TNF-α, and fecal calprotectin. This effect was thought to be related to curcumin's ability to inhibit NF-κB activation, regulate cytokine activity, increase PPAR-γ (Peroxisome proliferator-activated receptor gamma), and suppress STAT3 and MAPK (Mitogen-activated protein kinase) signaling pathways [36].

Qian Xiaobao and colleagues, in a clinical study of severe UC treated with a combination of Guben Yichang tablets and IFX, found that the combined therapy promoted the expression of epidermal growth factor receptor (EGFR) and trefoil factor 3 (TFF3), thereby accelerating mucosal healing, driving cell migration and proliferation, and inducing epithelial regeneration. The combined treatment group also showed higher levels of interferon-gamma (IFN-γ) and lower levels of IL-4 compared to the IFX-only group, further enhancing the modulation of immune cell activity [37].

Tan Gaozhan et al., in their study of the combination of Shaoyao Decoction and IFX for the treatment of severe UC, found that the combined treatment group showed a significantly greater reduction in TNF-α, platelet (PLT), and D-dimer levels compared to the IFX-only group. The mechanism may involve the dual action of reducing inflammatory factors and improving the hypercoagulable state, although further research is needed. Studies also indicate that Shaoyao Decoction may exert its anti-fibrotic effects by promoting PPAR-γ expression and inhibiting the TGF-β1/Smads signaling pathway, as well as suppressing epithelial-mesenchymal transition (EMT) [38,39].

Hu Bimei and colleagues, in their clinical study of elderly patients with steroid-refractory UC treated with a combination of Qingre Qushi Jianpi Huafu Decoction and IFX, found that C-reactive protein (CRP), PLT, erythrocyte sedimentation rate (ESR) were positively correlated with clinical symptoms such as abdominal pain, diarrhea, blood in stool, and gastrointestinal mucosal inflammation ($P<0.05$). After treatment, the experimental group had significantly higher rates of gastrointestinal mucosal healing than the control group ($P<0.05$), and there were also greater improvements in the levels of PLT, CRP, and ESR ($P<0.05$). The authors suggested that the effects were related to the anti-inflammatory and detoxifying properties of the decoction, combined with the way IFX interacts with inflammatory factors due to its solubility and transmembrane properties [40].

Liu Wei and colleagues, in their study of the combination of IFX and Anchang Yuyuan Decoction in UC treatment, found that the combined therapy more effectively reduced inflammatory cytokines and significantly elevated the levels of CD3+, CD4+, and CD4+/CD8+ ratios. Furthermore, the combined therapy demonstrated a more pronounced improvement in TCM symptomatology. Research suggests that Anchang Yuyuan Decoction promotes intestinal mucosal healing by activating the IL-13/JAK1/STAT6 signaling pathway and upregulating the expression of occludin and claudin-1 [41,42].

Tao Weiguo's clinical study on the use of Shenling Baizhu San combined with IFX in elderly UC patients revealed that after treatment, both serum D-lactate and endotoxin levels were significantly lower, and the observation group had significantly better mucosal imaging scores and disease activity index (DAI) scores than the control group ($P<0.05$). This improvement may be related to the ability of Shenling Baizhu San to regulate the autophagy pathway in intestinal epithelial cells through proteins such as phosphatidylinositol-3-kinase (PI3K), mammalian target of rapamycin (mTOR), and ubiquitin-binding protein-1 (p62) [43,44].

Currently, only infliximab (IFX) is approved for use in UC treatment in China. Thus, research on the combination of IFX and TCM for UC is still limited, and most studies remain at the clinical observation stage. There is a lack of in-depth research on the mechanisms underlying the combined therapy.

5. Discussion

Ulcerative colitis (UC) has high heritability and recurrence rates. In the past, the main therapeutic goal was symptom relief. However, as our understanding of the disease deepens, it has been found that even during periods of remission, the intestines may still experience damage and complications due to underlying (subclinical) inflammatory responses. As a result, there is an urgent need to find more effective treatments [45,46]. Targeted inhibition of TNF-α has provided a new direction for UC treatment, making the possibility of cure attainable. However, several issues remain unresolved in its clinical application, such as drug immunogenicity, the long-term efficacy and safety of the medication, and its impact on disease prognosis. Optimizing treatment regimens to improve efficacy and prognosis will be an important area of research for UC treatment.

A wealth of basic and clinical studies have confirmed the significant therapeutic effect of traditional Chinese medicine (TCM) on UC. Current research has shown that TCM works through multiple targets, pathways, and levels to prevent and treat UC. Specifically, it can regulate intestinal immune dysfunction, modulate the gut microbiota, combat oxidative stress, inhibit the release of inflammatory cytokines, repair the intestinal mucosal barrier, suppress pyroptosis, and regulate signaling pathways such as Notch, PI3K/Akt, and TLR4/NF-κB. These mechanisms provide theoretical support for using TCM in the prevention and treatment of UC [47]. However, research on the anti-inflammatory immune effects and molecular genetics of TCM is still in its early stages. Additionally, studies on the combination of TCM and anti-TNF-α monoclonal antibodies in UC treatment are currently limited to clinical observations, and there has been little exploration of the mechanisms behind this combination therapy by scholars worldwide.

Nonetheless, the advantages of combining Chinese and Western medicine in treating UC are clear. For example, the issue of opportunistic infections, which cannot be ignored in targeted therapies, can be addressed by TCM methods such as strengthening the body's resistance and expelling pathogens, tonifying qi, and stabilizing the exterior. Common clinical formulas include Shenling Baizhu San and Yupingfeng San. Intestinal fibrosis is an important cause of structural damage to the intestines in UC patients. TCM views qi and blood stagnation, damp-heat accumulation, and malnutrition of the intestinal collaterals as the primary pathophysiological mechanisms of intestinal fibrosis. The recommended treatment includes nourishing the blood, activating the collaterals, resolving dampness, and detoxifying. Clinical use of formulas like Danggui Shaoyao San and Wengjing Tang (with modifications) has yielded good results. Malnutrition is a common manifestation in UC patients, severely affecting their quality of life. TCM can help rebuild gastrointestinal function through methods such as tonifying the spleen and stomach and promoting qi circulation. Common clinical formulas include Buqi Yunyin Decoction and Xiangsha Liujunzi Decoction (with modifications).

At present, there are few high-quality studies on the combination of TCM and targeted TNF-α inhibitors in UC treatment, and these studies are still in the clinical observation phase. In the future, multi-center, high-quality studies on the integration of Chinese and Western medicine for UC should be conducted from various perspectives. These studies could explore the potential mechanisms of synergy between TCM and anti-TNF-α monoclonal antibodies, thus facilitating better combined treatment approaches for UC.

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