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Clinical Research Progress of Crohn

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Abstract

Crohn's Disease (CD) is a chronic recurrent inflammatory bowel disease with unknown etiology, most common in the terminal ileum and adjacent colon. In the past 30 years, the global prevalence of CD has continued to rise. Although the etiology is unknown, studies have shown that it is closely related to geographical environment, microfold cell damage, intestinal flora changes, epithelial barrier damage, immune dysfunction and low. The main clinical manifestations of CD are abdominal pain, chronic diarrhea, fatigue, fever and weight loss. At present, 5-aminosalicylic acid, antibiotics, glucocorticoids, immunosuppressants and biological agents are mainly used for treatment, but the drug effect is limited and the effect is not good. Recent studies have shown that Mesenchymal Stem Cells (MSC) can down-regulate immune response and promote tissue healing, which has certain safety and effectiveness in the treatment of moderate and severe CD, and has broad application prospects, but also has certain limitations. This paper summarizes the application and efficacy of related therapies in CD, providing a reference for clinicians.

Keywords

Crohn, Crohn's Drug Treatment, Mesenchymal Stem Cells

1. Introduction

Crohn's Disease (CD) is a chronic recurrent inflammatory bowel disease with unknown etiology, which can involve all digestive tracts from the oral cavity to the anus. It is most common in the terminal ileum and adjacent colon, showing segmental, asymmetric, transmural and nonspecific intestinal inflammatory diseases. It is a lifelong disease. Although treatments for Crohn's disease are increasing, the cure is still impossible. Moreover, since Crohn's disease is accompanied by complications such as perianal lesions and extraintestinal manifestations in addition to gastrointestinal symptoms, about 50% of Crohn's patients will undergo surgery at least once in their life, and even intestinal resection and

stoma surgery are needed in severe cases [1]. In recent years, the incidence of CD in China is increasing. The pathogenesis of CD anal fistula is not clear, and there are two hypotheses of ulcer fistula and anal gland infection [2]. This review, starting with the current treatment methods, aims to provide a reference for the rational use of Crohn's treatment, as follows.

2. Epidemiology

From the regional point of view, the global incidence of Crohn has increased by 4% - 15% every year in the past three decades, and the incidence of Crohn in the western industrialized countries is higher but tends to be stable [3]. The incidence in Europe and the United States is much higher than that in Asia and the incidence in cities is higher than that in rural areas, which may be due to more serious urban pollution and population distribution, which is more conducive to pathogen transmission. In terms of age, the onset age of Crohn showed a bimodal distribution. In Europe and the United States, the incidence of Crohn peaked between 20 - 30 years old and 60 - 79 years old. In most Asian populations, two peaks were 20 - 24 years old and 40 - 44 years old [4]. In epidemiological studies in China, the incidence of Crohn is high in young adults, and the second peak is not obvious [5]. From a gender perspective, the prevalence of Crohn in women in Europe and the United States is mostly higher than that in men, while in Asia it is the opposite. In the 2010-2014 Asian epidemiological survey, 72.4% of patients were men, and the risk ratio of men to women in our country was 1.15:1 [6] [7]. From the clinical manifestations, the distribution of Crohn's disease is uniform in the western population. About one-third of Crohn's disease occurs in the colon, ileum and ileum, 29% of Crohn's disease shows stenosis or penetration, and about 9% - 17% of patients with perianal disease. In contrast, Asian patients are mainly characterized by ileal lesions, and more than 50% of patients are accompanied by perianal lesions. The anal fistula is one of the most representative perianal lesions of Crohn's disease [8].

3. Etiology

First of all, the difference in diet structure is an important factor in CD, such as cold bacteria in frozen foods. Long-term and high-frequency use of non-steroidal anti-inflammatory drugs will also increase the risk of disease. In addition, studies have shown that smokers are more likely to suffer from CD [9]. In addition, microfold cell damage, intestinal flora changes, epithelial barrier damage, immune dysfunction and low will lead to its pathogenesis [10] [11] [12]. It is worth mentioning here that the destruction of microfold cell will enter the intestine through the basement membrane pore, and the pathogen will directly contact with related immune cells to induce immune response [13]. The most common ileocecal region of CD is the largest mesentery of human body, where fat is accumulated, and the mesentery of CD patients is thickened and shortened, and the adipose tissue is more likely to extend the encased bowel. Studies have shown that me-

senteric fat wrapping with fibrosis and muscularization are closely related to the pathogenesis of CD. In addition, compensatory hyperplasia of mesenteric lymph vessels caused poor lymphatic drainage, dendritic and antigen cell aggregation induced T cell immune response are possible causes of CD [14].

4. Pathological Features

The main pathological feature of Crohn's disease is inflammatory lesions throughout the intestinal wall. The main manifestations were mucosal congestion, edema, ulcer on the surface, fibrous exudation in the plasma membrane, corresponding mesenteric congestion, edema, mesenteric lymph node enlargement. Microscopically, edema was found in each layer of the intestinal wall, and the submucosal layer was the most obvious, with congestion, inflammatory cell infiltration, lymphatic expansion and tissue cell proliferation. With the development of the disease, there are many progressive ulcers or longitudinal fissure on the mucosal surface, deep into the muscular layer and can form sinuses with each other. The adjacent mucosa can be uplifted as paving stones due to submucosa edema and granulomatous hyperplasia. Xiao Shuyuan *et al.* [15] believe that the main feature of histopathological examination of Crohn's disease is chronic inflammatory cell destruction of mucosa and intestinal wall tissue. Crohn's disease generally has fewer granulomas and smaller granulomas with occasional multinucleated giant cells. Studies have shown that only 20% of patients with clinical pathological examination can find non-caseous granuloma [16].

5. Main Clinical Manifestations and Diagnosis of Crohn

Patients with Crohn's disease usually have symptoms lasting for several years before diagnosis, mainly manifested as abdominal pain, chronic diarrhea, fatigue, fever and weight loss. It also includes other symptoms, such as growth retardation or stagnation in children with Crohn, loss of appetite, weight loss, fever, fatigue, anal fissure, and some extraintestinal manifestations, such as joint swelling and pain, primary sclerosing cholangitis, osteoporosis, scleral inflammation, and oral ulcer [17]. CD diagnosis cannot rely solely on a certain index, need to combine symptoms, imaging, pathology, laboratory tests and other comprehensive judgment. Because intestinal mucosal lesions are one of the strong invasive manifestations of Crohn's disease, endoscopy plays an important role in the diagnosis of Crohn's disease, including colonoscopy, balloon-assisted enteroscopy, capsule endoscopy and so on. For patients with clinical symptoms suggesting Crohn's disease, the initial assessment should include colonoscopy. The characteristic manifestations that can be observed under endoscopy are leaping gastrointestinal lesions, mainly including erythema, erosion, ulcer, edema, stenosis, etc. Among them, longitudinal ulcer and paving stone-like changes are the most typical, and sometimes rare fistulas can be observed [18]. The role of enteroscopy in the initial assessment of suspected patients is limited, but when the

position is beyond the scope of fiber colonoscopy, balloon-assisted examination can be used for areas of concern [19]. The advantage of capsule endoscopy is its non-invasiveness and sensitivity. Some studies have shown that the diagnostic rate of capsule endoscopy is as high as 71%, but for intestinal stenosis, patients with obstruction may have a retention risk [20]. When colonoscopy is still unable to diagnose, pathological examination can sometimes play a key role, which is also one of the important links in the diagnosis of Crohn's disease. Its typical manifestation is non-caseous granuloma, but only about 20% of patients can be caught clinically, and this is not a unique pathological feature of Crohn's disease [21]. Clinicians can also diagnose Crohn's disease combined with imaging. Both computed tomography (CTE) and magnetic resonance enterography (MRE) can clearly show the intestinal wall, mucosa and complications outside the intestine, and help to distinguish between inflammatory stenosis and fibrosis stenosis.

6. Crohn's Drug Treatment

6.1. Aminosalicylic Acids

For example, sulfasalazine, usually 3 - 6 g per day, can be used for mild to moderate colon type patients, but not for isolated small intestinal type patients. The role of 5-ASA (5-aminosalicylic acid) in inducing remission of Crohn's disease has not been fully confirmed, so it is not recommended for the treatment of active Crohn's disease. In the course of remission, if the curative effect is not good, it is necessary to increase the dose or replace the treatment plan. Studies have shown that aminosalicylic acid drugs are effective in the treatment of UC (ulcerative colitis) and poor in the treatment of CD. In maintenance remission after hormone-induced remission, aminosalicylic acid drugs are effective for UC and ineffective for CD [22]. In addition, some studies have found that 5-ASA can inhibit the synthesis of *NF-κB* through peroxisome proliferator-activated receptor *γ* (*PPAR-γ*) pathway in mucosal epithelial cells, promote apoptosis, and exert anti-inflammatory and anti-tumor effects [23]. Therefore, aminosalicylic acid drugs play an important role in preventing UC carcinogenesis.

6.2. Glucocorticoids

For example: prednisone, methylprednisolone, etc., suitable for patients with moderate or above, can effectively control the symptoms and signs of Crohn's disease in a short time, in the induction of clinical remission effect is significantly higher than placebo. Hormone drugs are usually not recommended as maintenance therapy. The initial dosage is 0.75 - 1 g/kg per day, and then reduced weekly until withdrawal. The duration of medication generally does not exceed 12 weeks. Budesonide has also been proved to be able to be used for short-term induction treatment of moderately severe Crohn's disease. Compared with conventional hormones, budesonide has higher local anti-inflammatory ability and safety. Cao *et al.* [24] 42 patients with refractory CD were randomly divided into the observation group and the control group. Twenty-one patients

in the observation group were treated with thalidomide combined with glucocorticoid, and 21 patients in the control group were treated with conventional drug therapy. The study found that the peripheral blood PCT, CRP, ESR, PLT, CDAI score and SES-CD score of the two groups after treatment were significantly lower than those before treatment ($P < 0.05$). After treatment, the decrease of ESR and PLT in peripheral blood and the increase of HGB and ALB in the observation group were higher than those in the control group ($P < 0.05$). After treatment, the CDAI score and SES-CD score of the observation group were significantly lower than those of the control group ($P < 0.05$). After 72 weeks of treatment, the total effective rate of the observation group was 85.71%, which was significantly higher than 57.14% of the control group ($P < 0.05$). The total incidence of adverse reactions in the observation group was 42.86%, and the most common adverse reactions were not hand-foot numbness and sensory abnormalities. Zhang *et al.* [25] grouped 160 patients with moderate to severe active CD treated with glucocorticoid according to the proportion of eosinophils, in which 80 cases were in the eosinophil group (group A) with the proportion > 2%, and 80 cases were in the non-eosinophil group (group B) with the proportion ≤ 2%. After two months of glucocorticoid treatment, the clinical response rate, induction remission rate and mucosal healing rate in group A were higher than those in group B, and the difference in induction remission rate between the two groups was statistically significant ($P < 0.05$). After treatment, CRP, ESR, WBC and PCT of the two groups decreased, and the decrease of CRP and PCT in group A was more obvious than that in group B, and the difference was statistically significant ($P < 0.05$). Studies have shown that patients with moderate to severe CD with high eosinophils have higher clinical remission rate when receiving glucocorticoid treatment, and the decrease of CRP and PCT is more obvious, suggesting that we can treat CD according to the proportion of peripheral blood eosinophils as a biological indicator.

6.3. Immunosuppressants

Such as azathioprine, methotrexate, usually used as maintenance remission drugs. Among them, thiazoline is the first-line drug for the treatment of Crohn's disease. Due to the delayed onset of action, it is not recommended to be used as a drug for inducing remission in clinic. The efficacy of thiazoline as a maintenance treatment regimen is considerable, and the general target dose is 1.5 - 2.5 mg (kg·d). Shi Yanhong and Liu Zhanju [26] studies have found that immunosuppressive agents are still one of the main drugs for the treatment of CD. Therefore, grasping indications, reasonable dose, long-term and individualized application of immunosuppressive agents in the treatment of CD recurrence can still achieve better clinical efficacy.

6.4. Thalidomide

Thalidomide is an empirical drug used by some clinicians. It has immunoregulatory effect and can partially inhibit tumor necrosis factor-a (*TNF-α*) and inter-

leukin-12. The effect is slow and usually takes about 8 weeks. The recommended dose is 2.5 mg·kg/d. For patients with Crohn's disease with poor economic conditions, thalidomide can be a good choice for treatment, which is suitable for patients with ineffective or severe adverse reactions in the treatment of biological agents and maintenance treatment after the induction and remission of biological agents. A multicenter retrospective study in 2016 found that more than 50% of patients could achieve clinical remission in the first year. However, due to long-term use of thalidomide with limb numbness, pain and other adverse reactions, the proportion of patients with thalidomide discontinued due to toxicity after 12 months of treatment was more than 30%, and 46% at 24 months. More and more studies have shown that thalidomide, as an *anti-TNF-α* and anti-angiogenesis drug, has a good effect on refractory Crohn's disease [27]. Zhang Wanli *et al.* [3] randomly divided 56 adult patients with refractory Crohn's disease into observation group and control group. The total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$), and the incidence of adverse reactions and recurrence rate were significantly lower than those of the control group ($P < 0.05$). After 1 month, 6 months and 12 months of treatment, the Crohn's disease activity index (CDAI) scores of the two groups were significantly lower than those before treatment (all $P < 0.05$). After 6 and 12 months of treatment, the CDAI scores of the observation group were significantly lower than those of the control group at the same period ($P < 0.01$). At 1 month and 6 months after treatment, CRP level, white blood cell count and ESR in both groups were significantly lower than those before treatment (all $P < 0.05$); one month after treatment, CRP and ESR in the observation group were significantly lower than those in the control group ($P < 0.05$). At 6 months after treatment, the levels of CRP, white blood cell count and ESR in the observation group were significantly lower than those in the control group (all $P < 0.05$). This proves that the use of thalidomide in adult patients with refractory Crohn's disease has significant curative effect, can inhibit inflammatory response, reduce disease activity, reduce adverse reactions and recurrence, which is worthy of clinical promotion and research.

6.5. Biological Agents

The main biological agents, such as infliximab and adalimumab, are mainly suitable for patients with moderate to severe CD. Studies have shown that biological agents have more obvious effects in inducing and maintaining remission responses than placebo. The first biological agent to enter China is infliximab, which controls inflammation by binding to TNF. The dosage was 5 - 10 g/kg, and three induction treatments were performed at the 0th, 2nd and 6th weeks, and then injected once every eight weeks as maintenance treatment. The main clinical adverse events included allergic skin changes and opportunistic infections. When used as maintenance treatment, most patients relapsed after withdrawal, so long-term maintenance was needed [28]. In addition to infliximab, the current clinical use of biological agents for Crohn's disease, including adali-

mumab antibody, studies have shown that adalimumab maintenance therapy in patients with severe CD has a good effect [29]. These two types of drugs have been used in China since two years ago. Although their use time is short, their efficacy in improving symptoms and signs of Crohn's disease has been confirmed in foreign studies, and the incidence of adverse reactions of various antibiotics has no significant difference. The selection of biological agents needs to comprehensively consider the guidelines and consensus recommendations, the clinical characteristics of CD patients, the efficacy of biological agents, the safety of medication, pharmacoeconomics, and the wishes of patients. Under the condition of fully balancing risks and benefits, individualized treatment plans should be formulated [30].

6.6. Antibiotics

Etronidazole or ciprofloxacin is recommended more-general course of treatment is not more than 3 months. Studies have shown that antibiotics do not have the effect of inducing clinical remission and promoting mucosal healing, but are suitable for the treatment of complications, such as abdominal abscess. The postoperative use of antibiotics is helpful to prevent recurrence. Studies have shown that the therapeutic effect of different antibiotics in different parts of CD patients is different [31]. CD patients in different active period choose different antibiotics, also have different curative effect. Therefore, whether antibiotics need and type, dose, time choice, still need more clinical practice and evidence-based medical evidence. Therefore, the clinical application of antibiotics in the treatment of CD requires individualized treatment [32].

6.7. A New Treatment for CD Disease-Mesenchymal Stem Cells

The ultimate goal of Crohn's treatment is to achieve deep remission including symptom control and endoscopic mucosal healing, while maintaining a high quality of life. At present, the treatment of CD mainly lies in symptom control. When the drug treatment mentioned above fails, surgery is often required (including 5-aminosalicylic acid, antibiotics, glucocorticoids, immunosuppressants and biological agents). However, some patients refused or did not meet the surgical conditions (such as large-scale intestinal involvement, malnutrition, etc.). Stem cell therapy is another alternative method for the treatment of CD patients, mainly by changing mucosal immune response. The completed and ongoing studies have shown that stem cell therapy has a certain effect on some CD patients, which may increase a new disease treatment for CD patients.

At present, the mechanism of mesenchymal stem cells in the treatment of Crohn mainly includes immune regulation, polarization and homing, secretion of exosomes with cell communication, tissue repair and immunogenicity. At present, MSC for CD treatment mainly comes from adipose tissue, bone marrow and umbilical cord blood [33]. Bone marrow has always been the main source of mesenchymal stem cells, but the donation process is invasive. In addition, the survival time of mesenchymal stem cells derived from bone marrow is short, and

the differentiation potential of mesenchymal stem cells may be affected with the age of donors. Studies have shown that bone marrow mesenchymal stem cells can regulate Treg cells, migrate to inflammatory sites, and inhibit immune response [34]. Umbilical cord blood is relatively less likely to be successful in isolating mesenchymal stem cells than bone marrow, but the invasion of the separation process is lower and the proliferation of mesenchymal stem cells is stronger. In the past 10 years, adipose tissue mesenchymal stem cells have been used more and more in clinical practice, accounting for about 30%, as an important alternative source of mesenchymal stem cells in bone marrow and umbilical cord blood. The specific pathogenesis of CD is not clear, but its immune function plays an important role in the pathogenesis. MSC can maintain the barrier function of intestinal mucosa through growth factors and cytokines, so it is suitable for severe Crohn's disease when the treatment effect of glucocorticoids, immunosuppressants and biological agents is not good, especially for patients with complex refractory anal fistula CD [35]. MSC treatment is not suitable for patients with surgical treatment or surgical contraindications. Therefore, it is necessary to determine the disease status of CD patients before MSC treatment. At the same time, attention should be paid to the possibility of abdominal, pelvic abscess or other infections in patients.

At present, there is no uniform standard for the dose and course of treatment of CD by MSC in clinic. It to sentence case that Alvaro-Gracia *et al.* [36] found that when 20 million units of MSCs were used to treat CD patients with anal fistula as the initial dose, no clinical response was obtained, and 20 million units of MSCs were added again at 8 weeks of treatment, which eventually led to anal fistula closure. However, this study involved a small sample size and lacked multicenter large sample validation. The treatment of CD by MSC includes intravenous infusion, local injection, superior mesenteric artery injection, and femoral artery injection. Intravenous infusion is the most ideal way to inhibit MSC at this stage, especially for CD patients with anal fistula and rectovaginal fistula, which can promote the repair of lesion tissue and is easy to operate. However, due to the retention of drugs in the lungs, the proportion of drugs that can reach the intestinal inflammatory site is reduced, thereby reducing the therapeutic effect. Superior mesenteric artery injection and femoral artery injection are invasive operations, which increase the risk of infection and complications, but help to increase the drug concentration reaching the intestinal inflammatory site and have good therapeutic effect. Local injection only for local lesions has good effect, but the effect of systemic inflammation is general. Dave *et al.* [37] Studies have found that injecting human bone marrow MSCs from left ventricle into CD mice by ultrasound localization can increase the proportion of MSCs reaching inflammatory sites, and significantly reduce the incidence and mortality of mice. However, this treatment is not applicable to clinical patients and only has a certain reference value.

However, because stem cells have the typical characteristics of oncogene-activated tumor cells and can lead to their differentiation in the process of cell continuous

passage, whether mesenchymal stem cell transplantation can cause cancer has been concerned. At present, there is no clear understanding of this issue in the academic community. Some experts believe that mesenchymal stem cells will not cause tumor problems, but also effectively inhibit colonitis-related rectal cancer. Some studies believe that mesenchymal stem cells will have a transient low fever after transplantation, but there is no ectopic growth [38]. Portilla *et al.* [39] reported one case of uterine leiomyoma, but uterine leiomyoma was the result of multiple factors, so the study did not show that MSC treatment had a carcinogenic risk. In a study of colorectal cancer metastasis in obese patients, IL-6 secreted by ADSC (Adipose-derived mesenchymal stem cells) can promote tumor metastasis, and metastatic tumor cells further recruit ADSC. ADSC converts tumors into metastatic phenotypes by activating the STAT3 pathway. It suggests that patients with tumor history should not use MSC, which may increase the risk of tumor recurrence or metastasis. In general, MSC has good efficacy and safety in the treatment of CD, but its interaction with tumors is still unclear. Therefore, the clinical application of MSC should be very cautious for tumor patients.

7. Conclusion

To sum up, the CD is a chronic, progressive and destructive intestinal inflammatory disease, which is often accompanied by the intestinal canal and intestinal function damage. The treatment plan of patients should be determined according to the age of patients, suspected involvement sites, the severity of disease and recurrence risk. The comprehensive judgment of symptoms, imaging, pathology and laboratory examination should be combined to assist in the diagnosis and efficacy monitoring of CD. At present, no MSC treatment for CD is a very promising clinical scheme. MSC transplantation can delay the progression of CD, improve the quality of life of patients, and promote the recovery of the intestinal mucosa, with few adverse events. However, since MSC treatment of CD is still in the experimental stage, multi-center, large sample, randomized double-blind study is still needed. At the present stage, there are still some problems to be solved, such as the ideal source of MSC, the indications of CD patients, the ideal transplantation method, the number of treatments and the course of treatment, the changes in intestinal flora after treatment, how to deal with the ineffective treatment, whether the recurrence or aggravation of the disease after treatment continue to maintain MSC treatment and so on, which need to be deeply discussed in future clinical trials. The advantages and disadvantages of autologous or allogeneic mesenchymal stem cells for clinical treatment are also uncertain. It takes a long time to cultivate sufficient mesenchymal stem cells for autologous transplantation in vitro. Therefore, how to achieve large-scale expansion of mesenchymal stem cells in vitro is also the focus of future research. In general, MSC is effective and safe, but for tumor patients, in-depth basic research is still needed to reveal the therapeutic mechanism of MSC, and long-term clinical trial follow-up should be carried out to investigate its long-term safety.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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