

Research Progress of Traditional Chinese Medicine in The Treatment of Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is an autoimmune disease mainly characterized by joint synovitis, with complex etiology and pathogenesis, intractability and high disability, which affects patients' quality of life, physical and mental health seriously. With the in-depth research of traditional Chinese medicine (TCM) in the field of RA, Chinese medicine treats RA by etiology and pathogenesis analysis, syndrome differentiation, adopting internal treatment, external treatment, and combining internal and external treatments, the curative effect is remarkable. TCM treatment has unique advantages in effectively alleviating pain symptoms, slowing down the process of disease development and reducing adverse reactions efficiently. Based on the literature research, this article will review and summarize the etiology and pathogenesis of RA, Chinese medicine treatment methods, and modern research progress, as well as analyze the advantages and challenges of Chinese medicine in the treatment of RA, so as to provide reference value for the diagnosis and treatment of RA and contribute to new research directions and new drug development.

Keywords: traditional Chinese medicine, rheumatoid arthritis, internal treatment of traditional Chinese medicine, external treatment of traditional Chinese medicine.

1. Introduction

RA is an autoimmune disease, the etiology of which has not been clarified in western medicine. The main clinical manifestation is erosive, symmetric, progressive polyarthritis, which can lead to joint deformity, dysfunction, and systemic symptoms such as fever and anemia [1]. The global incidence of RA is 0.5%-1%, predominantly affecting the female, accounting for about 70% [2]. RA cannot be cured, which can only be treated to alleviate symptoms and delay the disease process. Currently, western medicine treats RA mainly with non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), glucocorticoids hormones, etc. [3]. However, the adverse effects of long-term use cannot be ignored.

The treatment of RA by TCM is safe, reliable and effective. It can reduce the adverse reactions caused by western medicine, such as neurotoxicity, cardiotoxicity, and drug resistance caused by long-term use of western medicine. So Chinese medicine treatment has a promising therapeutic application. At present, TCM continues to develop the research on the etiology and pathogenesis of RA, the therapeutic pathways and mechanisms of internal and external treatments of Chinese medicine and carry out clinical research verification. Therefore, the article will review the research progress, summarize the advantages and challenges of TCM in the treatment of RA, which will

provide a systematic reference value and direction for in-depth diagnosis and treatment research as well as the development of new drugs for RA.

2. Etiology and pathogenesis

RA belongs to the category of 'bi syndrome' (arthralgia) in TCM, which is attributed to the attack of external evil and the deficiency of healthy qi. The main pathological factors are wind, dampness, cold, heat, phlegm and blood stasis. Because of the deficiency of healthy qi, evil qi enters into the body and obstructs the flow of qi and blood, which leads to pain syndrome. The wind-cold-wet bi accumulates for a long time, forms into heat and become wind-damp-heat bi. Bi syndrome recurrent attacks and it's difficult to be cured. As the obstruction of stasis and phlegm, the joints can't be nourished so that leads to joint swelling, stiffness and limited flexion and extension. With the loss of qi and blood, the functions of the liver and kidneys diminish and cause deficiency bi [4].

Xuan and his group summarized the high difficulty of treatment and high disability rate of RA and concluded that RA is different from traditional pathogenesis of bi syndrome. The group propose the theory of double poison that includes external and internal pathogenic poison to explain the etiology and pathogenesis of RA. The theory is based on poison, emphasizing how violent the poison is and the important role it plays in RA [5]. The combination of traditional medicine with modern medicine through evil poison (wind, cold, dampness, heat, biochemical environment and other external factors) and latent poison (phlegm, blood stasis and other pathological products) provides a new way for RA treatment.

3. Traditional Chinese Medicine Treatment

TCM treatment of bi syndrome bases on the principle of eliminating evils, dredging

Meridian and relieving pain. TCM treats RA through syndrome differentiation analysis according to the nature of the disease and pathological products. For those who have a mixture of deficiencies and excess, both the symptoms and the root cause should be taken into account. Enhancing qi and blood supplementation, strengthening liver and kidney functions for the patients with chronic bi syndrome. TCM treatments include internal treatment, external treatment and combination of internal and external treatment.

3.1. Internal Treatment of Traditional Chinese Medicine

3.1.1. Common Chinese Herbal Medicines Used in The Treatment of Rheumatoid Arthritis

In view of the different pathogenesis of bi syndrome, using suitable Chinese medicine to eliminate wind and dampness, relax tendons and unblock meridians, alleviate pain, promote blood circulation and disperse blood stasis, nourish qi and blood. Commonly used traditional Chinese medicines include Qianghuo (Notopterygium root), Leigongteng (Tripterygium wilfordii Hook), Chuanwu (Aconitum Carmichaelii), etc.

Notopterygium root is bitter and pungent, which can alleviate dampness and wind, relieve joint pain and strengthen joints effectively. Modern research has shown that Notopterygium root mainly contains Notopterol and Isoimperatorin. Wang and his team are dedicated to the research on collagen-induced arthritis mouse model. The team validated that Notopterol can inhibit JAK2 and JAK3 kinase activity, suppress the JAK2/3-STAT signaling pathway, which plays an anti-inflammatory role and alleviates RA symptoms [7]. Isoimperatorin improves Th17/Treg imbalance and reduces inflammatory response in RA patients by participating in the regulation of Foxp3 expression by miR-34a [8].

Tripterygium wilfordii is bitter, cold and toxic. It has the functions of dispelling wind and removing dampness, promoting blood circulation and reducing swelling and relieving pain. *Tripterygium wilfordii* is the essential medicine for treating wind-damp-heat arthralgia, morning stiffness, tender, warm, swollen joints and chronic arthralgia caused by joint deformation. The main components of *Tripterygium wilfordii* are tripterygium glycosides. Pharmacological studies have shown that tripterygium glycosides play immunosuppressive and anti-inflammatory effects by inhibiting and antagonizing the release of inflammatory mediators and inhibiting the proliferation of T cells [9].

Aconitum Carmichaelii is pungent, bitter, hot, with great toxicity, especially effective in treating wind-cold-dampness bi. It has the function of dispelling wind and removing dampness, warming the meridian system and relieving pain. The main contents of *Aconitum Carmichaelii* are aconitine, Mesaconitine and Hypaconitine. Shao's experiment showed that aconitine can inhibit abnormal synovial hyperplasia in RA patients and improve RA symptoms by inhibiting the proliferation activity of RA-FLS and inducing apoptosis [10]. [9]Aconitine can also improve the pain threshold by increasing the 5-hydroxytryptamine levels in the brain and has an analgesic effect[11].

3.1.2. Common Prescriptions of Traditional Chinese Medicine Used in The Treatment of Rheumatoid Arthritis

Chinese medicine treatment of RA commonly used compound formulas include Guizhi Shaoyao Zhimu Decoction, Juanbi Decoction etc.

Guizhi Shaoyao Zhimu Decoction is one of the classic prescriptions of Synopsis of Golden Chamber, which has the efficacy of dispelling wind and removing dampness, warming yang for dispersing cold and treating the pain in limbs and joints. The main herbal medicines are Guizhi (Cinnamon Twig), Mahuang (Ephedrae), Fuzi (Monkshood), Baizhu (White Atractylodes Macrocephala), Fangfeng (Divaricate Saposhniovia Root) etc. Cinnamon Twig and Ephedrae play the role in expelling wind and cold evils. Monkshood can warm channels and expel cold. White Atractylodes Macrocephala is used with Divaricate Saposhniovia Root to dispel wind and dampness. Modern pharmacological studies have found that Guizhi Shaoyao Zhimu Decoction has anti-inflammatory, analgesic and immunomodulatory effects. The decoction plays a therapeutic role in reducing autoantibodies and inhibiting the level of inflammatory factors such as TNF- α , improving the imbalance of Th1/Th2 and enhancing the function of inhibitory neurons in the brain pain center [12].

Juanbi Decoction is composed of Qianghuo (*Notopterygium incisum*), Fangfeng, Danggui (Chinese Angelica), Huangqi (*Astragalus membranaceus*) etc. This decoction is used for win-cold-wet bi because of its function of benefiting qi and ying blood, dispelling wind and dampness. Chinese Angelica can promote blood circulation and remove meridian obstruction. *Notopterygium incisum* and Divaricate Saposhniovia Root dispel wind and remove dampness. *Astragalus membranaceus* can promote body liquid generation and nourish blood. Modern pharmacology shows that *Notopterygium incisum* and Divaricate Saposhniovia Root contain volatile oil, which has immunosuppressive, anti-inflammatory and analgesic effects. *Astragalus membranaceus* can regulate immune dysfunction [13]. The clinical studies of Shi showed that the expression levels of TNF- α and IL-6 in RA patients were reduced after treatment with Juanbi Decoction. This prescription has proved that it has the effect of inhibiting inflammation and alleviating RA symptoms [14].[11]

3.2. External treatment of Chinese medicine

External treatment of RA includes acupuncture, moxibustion, acupoint injection and so on. Common methods of acupuncture therapy include needle therapy and acupotomy therapy. Acupuncture

treatment can improve RA symptoms by regulating the levels of inflammatory cytokines and chemokines in order to regulate immune function [15].

The main acupuncture methods are filiform needling therapy, electroacupuncture and caloripuncture. These methods are used to stimulate specific parts or acupoints of the body, so as to stimulate the qi and blood of the channels and regulate the body function. The commonly used acupoints are Yinlingquan (SP9), Zusanli (ST36), Hegu (LI4) and Sanyinjiao (SP6). Moxibustion fumigates and warms certain parts of the body by moxa to treat disease, warm the meridian system and dispel cold, which has significant effects on chronic wind cold bi. Studies have shown that acupuncture and moxibustion play effective roles in inhibiting inflammation and synovial hyperplasia by reducing the expression of pro-inflammatory cytokines and regulating the expression of signaling factor pathways such as nuclear factor κ B [16]. [16] Acupotomy therapy has a dual therapeutic effect of acupuncture and local minimally invasive surgery. You et al. treated 112 patients with RA clinically as the research object. After acupotomy treatment, compared with monotherapy for RA patients, symptoms and joint function were significantly improved through the joint cavity and joint surface repair [17].

3.3. Combined Internal and External Treatment Methods

With the improvement and application of internal and external treatment methods of traditional Chinese medicine, the efficacy of the combined use of the two methods in the treatment of RA is remarkable. Liu collected 100 cases of RA patients and treated them by oral use and external application of *Tripterygium wilfordii*. Results showed that the patients' morning stiffness duration, joint swelling and pain index were significantly decreased through this method, which shortened the treatment time efficiently [18]. Zhang et al. observed the efficacy of the treatment of RA with liver and kidney deficiency syndrome through the combination of Duhuo Jisheng Decoction and external washing, which showed that the levels of EsR, cRP, and IL-6 of the patients were lower than those before treatment. Besides, the efficacy was significantly better than that of the control group taking Western medicine methotrexate and hydroxychloroquine sulfate [19].

4. Modern Research Progress

4.1. Mechanism of Traditional Chinese Medicine Treatment for Rheumatoid Arthritis

TCM interferes in the inflammatory reaction mediated by multiple signaling pathways, including RANKL/RANK/OPG, PI3K-Akt, JAK/STAT and other signaling pathways [20]. RANKL/RANK/OPG signaling pathway affects the balance of bone resorption and bone formation by regulating the differentiation, maturation and apoptosis of osteoblasts and osteoclasts. Modern studies have shown that Guizhi Shaoyao Zhimu Decoction reduces the ratio of RANKL/OPG through this pathway, inhibits bone destruction and improves the disease [21]. By regulating the proliferation and apoptosis of synovial fibroblasts, the PI3K/Akt signaling pathway affects synovial hyperplasia and joint destruction, promotes the formation of osteoclasts and aggravates bone damage. Sinsinine can promote joint protection and immunosuppression via this pathway, and alleviate RA. JAK/STAT pathway is an important target for the treatment of RA. Yan Guoqiang et al. showed that the Tongbi capsule could inhibit Jak2/Stat3 protein phosphorylation, the production of inflammatory factors and chemokines, and the destruction of bone tissue, which play a positive role in the treatment [23]. Wang Jinfeng et al. treated RA by studying the regulation of Th17/Treg balance in TCM, indicating that TCM reduces the inflammatory response induced by Th17 by inhibiting the recruitment of Th17 from CD4⁺ T cell differentiation. TCM can inhibit osteoclast differentiation, promote osteoblast proliferation and reduce osteoarticular destruction [24]. CHEN et al. clarified the regulatory mechanism of RA from the perspective of miRNA and showed that tripterygium glycosides inhibited

inflammatory response, alleviating RA symptoms, and reduced disease activity by down-regulating the expression of miR-146a [25].

4.2. Effectiveness of Integrated Chinese and Western Medicine Treatment

With the increasingly mature research on the mechanism of TCM in the treatment of RA, the combination of Chinese and Western medicine has become an inevitable trend, with significant efficacy in shortening the morning stiffness duration, and relieving joint swelling and pain compared with single western medicine or TCM treatment.

Jiang et al. treated RA with methotrexate and hydroxychloroquine combined with TCM fumigation, [24]. According to the clinical study of Guizhi Shaoyao Zhimu Decoction combined with Western medicine methotrexate in the treatment of RA by Lee Kuan Yew, the delayed progress of bone destruction in the Chinese and Western medicine group was superior to that of single Chinese medicine treatment [27]. When traditional Chinese medicine is used in combination with methotrexate and other drugs, it can also reduce the body's resistance to methotrexate. When the external treatment of TCM is combined with Western medicine, the symptoms of RA patients can be better alleviated by regulating the immune function of the human body, reducing inflammatory factors and inhibiting inflammation. Guo Wenhui explored the clinical efficacy of acupuncture combined with TCM fumigation to assist conventional Western medicine in the treatment of RA. The morning stiffness duration in the treatment group of external Chinese medicine combined with Western medicine was significantly shorter than that in the treatment group of Western medicine only, which effectively improved the clinical symptoms of RA, reduced the integral optic density of MMP-3 and the levels of rheumatoid factors IgM-RF and IgM-RA in synovial fluid samples and alleviated inflammation. The therapeutic effect was significant [28]. Yu Jiali through the collection of hospitals within one and a half years of RA patients, the treatment group with ginkgo tablet combined with methotrexate tablet, and diclofenac sodium enteric-coated tablet treatment, while the control group was treated with Western medicine alone. The results showed that the total effective rate of the treatment group was 79.54% and that of the control group was 56.25%, which was significantly better than that of the control group ($P < 0.05$). It proved that the clinical effect of combined treatment of Chinese and Western medicine was significant [29].

5. Advantages and Challenges of Traditional Chinese Medicine in Treating Rheumatoid Arthritis

At present, western medicine is mainly used in the clinical treatment of RA, which has the disadvantages of easy relapse after drug withdrawal, stronger toxic and side effects, etc. For example, Chloroquine is used in the treatment of RA for the long treatment cycle, which can cause cardiotoxicity, neurotoxicity, nervous system and endocrine system adverse reactions, etc.

TCM comes from a wide range of sources, most of which are cheaper than Western medicine and have fewer side effects. Through syndrome differentiation and diagnosis, RA patients can receive individualized treatment for different syndrome types. TCM treatment or integrated Chinese and Western medicine treatment can alleviate the adverse reactions caused by long-term use of Western medicine, and reduce the dependence of patients on Nonsteroidal Antiinflammatory Drugs(NSAIDs),and glucocorticoids. The application of TCM can also reduce the body's resistance to Western medicine and has a great curative effect and application value.

Currently, RA cannot be completely cured and there are many challenges in the treatment of RA with TCM, which has a complex pathogenesis. Besides, the TCM diagnosis can be a composite pathogenesis, which needs to be treated according to the specific situation. Most of the Chinese medicine used in RA are rattan and insect medicine. Rattan medicine is highly toxic, such as

tripterygium glycosides, the main component of *Tripterygium wilfordii*, which has side effects such as liver toxicity, gonadal inhibition, and myelosuppression. It is necessary to pay attention to the dosage when using this kind of medicine and not abuse it. [27]Some patients do not accept insect drug treatment, which affects the feasibility and effectiveness of treatment.

TCM is empirical medicine. For the moment, the treatment of RA by TCM is mostly prescribed by clinical experiences, with insufficient scientific verification and mixed-quality of clinical studies. More high-quality clinical studies are needed. Therefore, measures should be taken like performing in-depth research on the mechanism of Chinese medicine treatment of RA, combining it with modern medicine, breaking the limitations of TCM therapy, using artificial intelligence to analyze patient data, providing individualized treatment plans, performing intelligent detection to assist Chinese medicine treatment in all aspect and fully leverage the unique advantages of TCM in treating RA.

6. Conclusion

With the increasing international recognition of TCM treatment, basic research and clinical research on RA continue to develop and progress. The treatment of RA by TCM has become an important therapeutic research direction. By providing a personalized treatment plan, selecting internal treatment, external treatment, internal and external combination, combination of Chinese and Western medicine treatment and other methods, TCM can reduce adverse reactions and side effects in the treatment process, effectively alleviate the symptoms of RA patients in the acute attack period, slow down the disease progress, with satisfactory curative effect and lower cost than long-term use of western medicine, which is of extraordinary significance for the treatment of RA. However, due to the limited research mechanism of TCM treatment of RA and insufficient scientific verification of clinical medicine, TCM needs to strengthen experimental study and clinical validation, save treatment costs and reduce toxic side effects and lighten the psychological and economic burden of RA patients. New drug development and application should be encouraged. Early diagnosis of RA is extremely important, actions should be taken to promote early detection of disease. Such as the development and application of RA diagnosis and monitoring kits based on multiple microRNA, which can assist TCM play its unique advantages of ‘preventing disease before it occurs and preventing disease from developing’ and improve the value of TCM in the clinical treatment of RA.

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