

# Clinical and Basic Research on Treatment of Rheumatoid Arthritis with Qing Re Huo Xue Decoction

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## Abstract

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by autoimmune overactivation, joint synovitis and bone destruction. The disease has a high disability rate, and the destruction of articular cartilage and bone is the main cause of disability. Traditional Chinese medicine has a good effect on the delay of bone destruction. Qing Re Huo Xue Decoction (composed of Rhizoma *Atractylodes*, Cortex *Phellodendri*, Radix *Salviae miltiorrhizae*, etc.) is an effective prescription for the treatment of rheumatoid arthritis in our department. We explained the effect of Qing Re Huo Xue Decoction on bone protection in rheumatoid arthritis from two aspects of clinical research and basic research. In order to provide a new reference for the prevention and research of rheumatoid arthritis.

**Keywords:** Basis; Clinical; Qing Re Huo Xue Decoction; Rheumatoid Arthritis

## Introduction

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by autoimmune overactivation, joint synovitis and bone destruction [1]. The disease has a high disability rate, and the destruction of articular cartilage and bone is the main cause of disability. The normal bone tissue of the body is in the dynamic balance of bone resorption caused by osteoclasts and bone formation caused by osteoblasts, and once the balance is broken, the development and growth of bones will be abnormal [2]. Chinese medicine has a good effect on delaying bone destruction. Qing Re Huo Xue Decoction (composed of Rhizoma *Atractylodes*, Cortex *Phellodendri*, Radix *Salviae miltiorrhizae*, etc.) is an effective prescription for the treatment of rheumatoid arthritis in our department. We explained the effect of Qing Re Huo Xue Decoction on bone protection in rheumatoid arthritis from two aspects of clinical research and basic research.

## Clinical Research

We randomly divided 78 patients with RA who were present at our department from July 2007 to December 2008 and divided them into 2 groups of 39 patients each. The Chinese medicine group was given Qing Re Huo Xue Decoction orally, and the Chinese and Western medicine group was added on the

basis with the western medicine Methotrexate (MTX) 10mg, MTX oral once a week. Two groups of patients were assessed for Health Assessment Questionnaire (HAQ) and Disability Related Scale (HAQ-DI) scores before treatment and 24, 52, 78 and 104 weeks after treatment. Results 24 weeks after treatment, the scores of HAQ and HAQ-DI of both groups were significantly lower than those before the treatment. The scores of HAQ and HAQ-DI continued to decline after 52, 78 and 104 weeks of treatment, and there was no statistically significant difference between the 2 groups. This indicates that Qing Re Huo Xue Decoction has a long-term and lasting effect on improving the quality of life of RA patients at the active stage and can slow down the occurrence of disability [3]. From July 2007 to March 2009, 86 patients with active RA who belonged to damp heat and blood stasis syndrome were randomly divided into the Chinese medicine group and the Chinese and Western medicine group, with 43 cases in each group. The Chinese medicine group was treated orally with Qing Re Huo Xue Decoction, and the Chinese and Western medicine group added MTX based on Chinese medicine for 12 months. X-ray evaluation was performed on 21 cases in the Chinese medicine group and 21 cases in the Chinese and Western medicine group. There was no statistical difference in gender and course of disease between the two groups. Two hand X-ray films were collected before treatment and 12 months after treatment. The chronological sequence and clinical data were hidden from the readers and the X-ray films were scored using the Sharp/van der Heijde method.

## Results

There was no significant difference in changes of bone erosion, joint space stenosis, and other changes seen in the hands of the Chinese medicine group and the Chinese and Western medicine groups at the one-year time point compared with those before treatment, and there was no significant difference between the two groups. This indicates that the progress of bone destruction in RA patients in the Chinese medicine group and the Chinese and Western medicine group is similar, indicating that Chinese medicine has potential protective effect in RA treatment in the medium and long term [4]. 142 cases of RA patients with damp heat and blood stasis syndrome were randomly divided into the Chinese medicine group and the Chinese medicine + MTX group, with 71 cases in each group. The Chinese medicine group was treated orally with Qing Re Huo Xue Decoction; the Chinese medicine +MTX group was treated with oral MTX based on the Chinese medicine group, each time 10mg, once a week, and both groups were treated for 24 weeks.

The Disease Activity Score (DAS28) and the American College of Rheumatology (ACR) response criteria were used as efficacy evaluation indicators at 0, 4, 12, 24 weeks of treatment, and adverse reactions were observed. Results after 12 weeks of treatment, the DAS28 scores of the two groups were significantly lower than before treatment. After 24 weeks of treatment, the DAS28 scores of the two groups were also significantly lower than those at 4 weeks of treatment. After 12 weeks of treatment, the ACR20 and ACR50 compliance rate of Chinese medicine + group was significantly higher than that of Chinese medicine group. With the exception of C-Reactive Protein (CRP) and dynamic Erythrocyte Sedimentation Rate (ESR), the indicators in the ACR reaction standards of the two groups were further improved with the prolongation of treatment time. In CRP, the Chinese medicine+MTX group had a quicker onset, and it began to decrease after 4 weeks of treatment. Both groups showed a slow onset of ESR, and it decreased after 12 weeks of treatment. The incidence of adverse reactions in Chinese medicine group was lower than that in Chinese medicine +MTX group. It is proved that the use of Qing Re Huo Xue Decoction alone can effectively control disease activity and improve rheumatic conditions, and has better safety than combined with MTX. Early recommendation is to jointly use MTX to improve the condition [5].

## Basic Research

Primary Rheumatoid Arthritis Fibroblast-Like Synoviocytes (RA-FLS) were prepared from the synovial tissues from patients with Rheumatoid Arthritis (RA), and the migration and adhesion of RA-FLS was induced by tumor necrosis factor alpha (TNF-alpha). Set blank group (without drugs and TNF- $\alpha$  intervention), induction group (10 or 20 ng / ml TNF- $\alpha$  induction), Qing Re Huo Xue Decoction low, middle, and high dose group (20, 100, 500 ng / ml Qing Re Huo Xue Decoction + TNF- $\alpha$  induction), 3 cases per group. The cell migration distance and area, cell adhesion OD value and adhesion inhibition rate were detected in each group, and the expression of PI3K/Akt signaling pathway related protein (PI3K,

p-Akt, Akt) in the cells was detected. Results Compared with the blank group, the migration distance and area of the induction group increased, the OD value of adhesion increased, and the expression of PI3K and p-Akt protein increased. Compared with the induction group, each dose group of Qing Re Huo Xue Decoction could inhibit the migration and adhesion of cells and PI3K, p-Akt protein expression. It was shown that Qing Re Huo Xue Decoction may inhibit the migration and adhesion of RA-FLS by down regulating the expression of PI3K and p-Akt protein in RA-FLS, thus slowing down the progress of synovitis and joint destruction [6]. 46 SD rats were randomly divided into normal group, model group, Qing Re Huo Xue Decoction group and methotrexate group. After the model was successful, serum IL-17 expression in rats was observed after regular intragastric administration for 6 weeks. Results Compared with the model group, serum IL-17 content in the Qing Re Huo Xue Decoction group was significantly lower than that in the model group, indicating that the bone protection effect of Qingre Huoxue decoction in inhibiting RA bone destruction may play a role by reducing IL-17 expression [7].

## Discussion

RA is a systemic disease. Synovitis is the most characteristic pathological change of RA. Synovial cells can secrete a variety of cytokines and proteases directly or indirectly involved in angiogenesis, cartilage and bone destruction. FLS is the main effector cell in synovitis, its abnormal proliferation is closely related to the progress of synovitis. Long distance migration of RA-FLS may lead to its mediated erosion and inflammation affecting the unaffected joints, and RA-FLS can migrate by adhesion to endothelial cells or extracellular matrix [8]. Therefore, inhibiting the abnormal migration and adhesion of RA-FLS can slow down cartilage destruction and protect uninvolved joints. Each dose group of Qing Re Huo Xue Decoction can significantly inhibit its adhesion and prevent RA-FLS migration and adhesion to cartilage and endothelial cells, thereby inhibiting synovial inflammation and cartilage destruction. IL-17 acts on osteoclast-differentiated supporting cells, such as synovial fibroblasts and osteoblasts, allowing it to express RANKL, thereby promoting osteoclast differentiation [9]; leading osteoclast hyper function: IL-17 It can trigger osteoclast hyper function through a wide range of pro-inflammatory and other cytokine pathways [10]. Therefore, reducing IL-17 levels is considered to be a promising treatment for the improvement of inflammatory diseases [11]. Qing Re Huo Xue Decoction can reduce the level of IL-17 in serum and inflammatory fibroblast synoviocytes of CIA model rats. According to the core role of IL-17 in synovitis, Qing Re Huo Xue Decoction blocks the important link of the inflammatory process and inhibits the hyperactivity of osteoclast, so it is not difficult to infer the mechanism of action that slows down or inhibits the process of RA bone destruction. Above from two aspects of clinical and basic interpretation of Qing Re Huo Xue Decoction anti-inflammatory for the treatment of RA and reduce bone destruction and the scientific hypothesis of Qing Re Huo Xue Decoction can “protecting bone” make the basic theory of RA Chinese medicine treatment have a certain breakthrough, and enrich the theory of the treatment of RA

in traditional Chinese medicine. The treatment of RA theory is an important theoretical exploration of traditional Chinese medicine therapeutics in basic research.

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