JTCM 中医杂志 Journal of Traditional Chinese Medicine

Online Submissions: http://www.journaltcm.com
info@journaltcm.com

J Tradit Chin Med 2015 October 15; 35(5): 487-498
ISSN 0255-2922

CLINICAL STUDY

Efficacy and safety of Xinfeng capsule in patients with rheumatoid arthritis: a multi-center parallel-group double-blind randomized controlled trial

Liu Jian, Wang Yuan, Huang Chuanbing, Xu Jianhua, Li Zhijun, Xu Liang, He Liyun, Sun Yue, Wang Yali, Xu Shengqian, Zhao Ping, Mao Tongjun, Tan Bin, Zhu Fubing, Zhang Pingheng, Fang Li

Liu Jian, Wang Yuan, Huang Chuanbing, Sun Yue, Wang Yali, Tan Bin, Zhu Fubing, Zhang Pingheng, Fang Li, Department of Rheumatism Immunity, The First Affiliated Hospital, Anhui University of Chinese Medicine, Hefei 230031, China

Xu Jianhua, Xu Shengqian, Department of Rheumatism Immunity, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

Li Zhijun, Zhao Ping, Department of Rheumatism Immunity, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233004, China

Xu Liang, Mao Tongjun, Department of Rheumatism Immunity, The First Affiliated Hospital of Wannan Medical College, Wuhu 241001, China

He Liyun, The Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China

Supported by the Key Projects in the National Science & Technology Pillar Program in the Twelfth Five-Year Plan Period: Clinical Research on Xin'an Medicine Prevention and Treatment of Difficult Diseases of Chinese Medicine (No. 2012BAI26B02). ClinicalTrials.gov Identifier: NCT01774877

Correspondence to: Prof. Liu Jian, Department of Rheumatism Immunity, The First Affiliated Hospital, Anhui University of Chinese Medicine, Hefei 230031, China. liujianahzy@126.com

Telephone: +86-13955109537

Accepted: September 9, 2015

Abstract

OBJECTIVE: To evaluate the efficacy and safety of Xinfeng capsule in patients suffering rheumatoid arthritis (RA).

METHODS: A multi-center parallel-group designed, double-blind, randomized, controlled trial was conducted. Totally 304 RA patients were assigned to two groups: one group was administered Xinfeng capsule (XFC) plus the placebo of leflunomide and the other given leflunomide (LEF) plus the placebo of XFC for twelve weeks. The clinical and laboratory parameters were compared at baseline and fourth, eighth, and twelfth weeks.

RESULTS: After twelve-week treatment, patients in two groups all showed some trend of effectiveness when compared in terms of American Rheumatism Association (ACR) recommended 20% , 50% , 70% improvement criteria, but it was insignificant. The validity in ameliorate modified disease activity score (DAS28) and laboratory indexes as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) were also found no difference. The score of health assessment questionnaire (HAQ), self-rating anxiety scale (SAS), self-rating depression scale (SDS) and quality of life questionnaire with rheumatoid arthritis (RAQOL) both lower than the first week and the changes showed no difference. However, the score of SDS dropped more in XFC group than in the other. A total of 147 adverse reaction cases were reported, which shows no difference between the two groups. The most common adverse reactions were hepatic impairment, anemia, leukocytopenia, epigastric discomfort and phalacrosis.

CONCLUSION: XFC demonstrated better improvement in the scores of SDS and compared with those of LEF group.

Key words: Arthritis, rheumatoid; Xinfeng capsule; Treatment outcome; Multicenter study; Double-blind method; Randomized controlled trials

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease which characteristically presents as a gradual symmetry, multi-arthritis. There has associated loss of joints' function, 50%-90% patients will occur radiographic joint destruction in the first 1 or 2 years.[1] Although disease activity may fluctuate, it will, if untreated, usually lead to joint destruction with erosive cartilage and bone damage, and potential tendon rupture.[2] At the mean time, RA is a multi-system disease, with the prevalence of extra-articular manifestations estimated to occur in up to 21.5% of patients with established disease,[3] that associated with an unfavorable outcome. During the last decade we have experience exciting developments regarding the approval of new treatment options, the advent of biological agents and disease-modifying anti-rheumatic drugs (DMARDs) (including leflunomide, methotrexate, sulfasalazine, azathioprine, et al) have made a profound impact on the outcome and prognosis of RA[4] In effect, DMARDs slow the disease process by modifying the immune system in some way.

Leflunomide (LEF) is an oral immunomodulator agent, which has been evaluated in RA in clinic and experiment.[5] Leflunomide is a competitive and reversible inhibitor of the mitochondrial enzyme dihydroorotate dehydrogenase restricting DNA and RNA synthesis in activated lymphocytes by diminishing pyrimidine availability and preventing cells from entering the S phase of the cell cycle. It can also inhibit protein tyrosine kinases in proliferating T and B lymphocytes with a commensurate decline in immunoglobulin synthesis.[6]

Recently, the traditional DMARDs still be recommended in the treatment of RA.[7] The increasing cost of biologics in this era of disease management led us to devise a treatment regime, optimal for use in a developing country like China, which was economical as well as effective in controlling disease activity.

LEF is one of immunosuppressants to cure RA in current. It is that to inhibit dihydrogen orotic acid dehydrogenase activity to affect the pyrimidine nucleotide synthesis pathway, and through inhibit tyrosine kinase activity to restrain T cell activation signal transduction. Its metabolites can affect the production of synovial fibroblasts of metalloproteinases, and it may inhibit the nitric oxide synthesis of the body to achieve the immunoregulation effect. However, these available medications may not work for everyone. Some high prices drugs make patients unable to long-term maintenance treatment. Therefore, it still needs to study novel anti-rheumatic drug.

Xinfeng capsule (XFC) as one of Chinese patent medicine which produced by our hospital, has been widely used in the clinical treatment of RA. XFC had been approved as a kind of hospital preparations by the Anhui Province Food and Drug Administration in 1997, then renamed the Fufangqiyi capsule in 2005 (drug approval number: Anhui medicine system Z20050062). Drug has good manufacturing practice and quality control. The high-performance thin-layer chromatography (HPTLC) fingerprint chromatographic for the evaluation of XFC has shown in the previous study.[8]

Our preclinical studies showed that XFC have a definite effect on relieving symptoms of joins in RA patients.[9-13] XFC can improve joint pain, swelling, and early morning stiffness, and it can also improve extra-articular manifestations such as anemia, platelet disease, lipid metabolism disorder, cardiopulmonary function, depression and quality of life. In addition, there is no adverse reaction of gastrointestinal disturbance and hepatorenal function damage reported. Lab studies have shown that[14-19] XFC can reduce paw swelling and AI of AA rats, and can improve the cardiopulmonary function and behavior of AA rats. The possible mechanism is the modulation of TGF-β1/Smads, Notch-Jagged/Delta and several other signaling pathway in regulating inflammatory/anti-inflammatory cytokines interacting. Thus XFC can regulate the expression of T regulatory cell (Treg) and forkhead box P3 (Foxp3), reduce the deposition of immune complexes and reduce the inflammatory reaction in tissue. These study data supported that XFC deserve further research as a potential Chinese medicine compound preparation for RA treatment. This clinical trial carried out simultaneously in 4 clinical research centers, which conducted in a randomized, double-blind, double parallel controlled method. Chinese Academy of Traditional Chinese Medicine was responsible for schema optimization, quality control and outcome assessment.[20] This study reported the result after treatment for 12 consecutive weeks, and described the clinical outcomes, efficiency, and adverse reactions of XFC.

PATIENTS AND METHODS

Patients

Eligible patients should be ≥18 and ≤65 years old and should have been diagnosed as active stage of RA based on American Rheumatism Association (ACR) 1987 revised criteria[21] and classified into functional class Ⅰ, Ⅱ or Ⅲ, according to Modified Disease Activity Score (3 variables) (DAS28-3)[22] promulgated by the European Union of anti-rheumatism. The disease activity of RA patients and classification is judged by DAS28-3. Patients were excluded if they were taking corticosteroids (≤ 15 mg prednisone or Equivalent) ≥ 4 weeks before entering the trial or they have high disease activity (DAS28-3 scores > 5.1) or they have diagnosed any other chronic inflammatory disease or connective tis-