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CLINICAL STUDY

Effect of Sanhuangyilong decoction plus methotrexate on tumor necrosis factor alpha and interferon gamma in serum and synovial fluid in rheumatoid arthritis patients with symptom pattern of damp heat obstruction

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Abstract

OBJECTIVE: To investigate the effect of Sanhuangyilong decoction plus methotrexate (MTX) on Interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) in the serum and synovial fluid of rheumatoid arthritis (RA) patients with damp-heat-obstruction symptom pattern, Sanhuangyilong decoction and the role of TNF-α and IFN-γ in the development of RA.

METHODS: RA inpatients with damp-heat-obstruction symptom pattern (partly with knee joint effusion) were selected as the research subjects. Before the treatment, healthy subjects and osteoarthritis (OA) patients with knee joint effusion were assigned to the serum control group and the synovial fluid control group, respectively; during the treatment, RA patients with damp-heat-obstruction symptom pattern were divided into two groups: one is combined group that was administered Sanhuangyilong decoction plus MTX; the other group was MTX group that received MTX only. The expression levels of TNF-α and IFN-γ in the serum and synovial fluid were measured with enzyme-linked immunosorbent assay (ELISA) before and after the treatment, and the peripheral blood levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and disease activity score in 28 joints (DAS28) were determined.

RESULTS: Before treatment, the serum levels of TNF-α and IFN-γ in the RA patients with damp-heat-obstruction symptom pattern were higher than those in healthy control group ($P < 0.05$).The expression levels of TNF-α and IFN-γ in the synovial fluid of the RA patients were higher than those in the serum of the RA patients ($P < 0.05$). The expression levels of TNF-α and IFN-γ in the synovial fluid of the RA patients were higher than those of the sy-

novial fluid of the osteoarthritis patients ($P < 0.05$). The expression of TNF-α and IFN-γ in the serum and synovial fluid of the RA patients had no correlation with the inflammatory activity index ESR, CRP, or DAS28 ($P > 0.05$). After 2 weeks of treatment, the expression level of TNF-α and IFN-γ in the combined group had increased, although the difference was not statistically significant ($P > 0.05$); in contrast, ESR, CRP, and DAS28 decreased, and the difference was statistically significant ($P < 0.01$). After 4 weeks of therapy, TNF-alpha and IFN-γ, ESR, CRP, and DAS28 in the combined group decreased compared with the before-treatment levels ($P < 0.01$). After 2 w of treatment, the differences in the TNF-α and IFN-γ expression levels in the combined group were not statistically significant ($P > 0.05$) compared with that in the MTX group, although there were statistically significant differences in the ESR, CRP, and DAS28 ($P < 0.05$). After 4 weeks of treatment, differences in TNF-α, IFN-γ, ESR, CRP, and DAS28 in the combined group compared with MTX group were statistically significant ($P < 0.01$).

CONCLUSION: TNF-α and IFN-γ might be involved in the development of RA. The RA patients with damp-heat-obstruction symptom pattern show better benefits from the treatment of Sanhuangyilong decoction plus MTX, and the treatment is superior to that of using MTX only.

Key words: Arthritis, rheumatoid; Dampness-heat; Cytokines; Blood sedimentation; C-reactive protein; Methotrexate; Sanhuangyilong decoction

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by chronic, erosive arthritis, which primarily involves symmetrical polyarticular swelling, pain, stiffness and multi-system involvement. The pathogenesis of RA is not clear. Research reports show that Th1 (T helper 1) and Th17 (T helper 17), the main pro-inflammatory Th subgroup, induce the pathogenesis of RA,[1] and many cytokines secreted by them play an important role in the pathogenesis of RA. Interferon gamma (IFN-γ) is the major cytokine secreted by Th1 cells; however, tumor necrosis factor alpha (TNF-α) is predominantly secreted by Th17 cells. Both cytokines play a specific role in the pathogenesis of RA. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are commonly used to reflect the disease activity of RA as clinical and laboratory indexes, and the disease activity score in 28 joints (DAS28)[2] is a comprehensive index for evaluating RA disease activity.

Based on the symptoms patterns minified in RA patients, in terms of theory of Traditional Chinese Medicine (TCM), RA is often diagnosed as the obstruction of *Qi* and blood in the meridians due to the invision of external pathogenic wind, cold, wet and heat, manifested as soreness, pain, numbness, a heavy sensation, swelling of the joints and limbs, limitation of movement and the formation of chronic inflammation. The Bi (symptom) pattern in Plain Questions[3] states that "if the wind, cold and dampness invade the body together, Bi (symptom) pattern might develop", demonstrating that Bi (symptom) pattern is associated with several pathogenic *Qi*. Shuo Wen Jie Zi[4] which was written in the Han Dynasty, includes the interpretation of "Bi, the pathogenic dampness", which indicates that pathogenic dampness is a major cause of rheumatism. The highest moisture levels in China occur in the Southwest. From 1993-1995, meteorologists investigated Beijing, Shanghai, Chengdu, and Guangzhou, which are in the north, southeast, southwest, and south of China, respectively, and the results show that the annual average relative humidity is 53% , 75% , 82% and 75%, respectively.[5] The view that "dampness and heat, arthralgia" is described as early as in the "synopsis of prescriptions of the Golden Chamber",[6] including the hypotheses that "patients suffering from pathogenic dampness have pain and fever" and "dampness being the disease, [which is] manifested as pain and fever of the body". Zhang *et al* [7] noted that the dampness-heat symptom pattern was closely related with the occurrence, development and prognosis of a variety of rheumatic diseases. In Traditional Chinese Medicine (TCM), RA is divided into 6 symptom patterns: damp-heat, phlegm and blood stasis, a deficiency of *Qi* and *Yin*, cold dampness, blood stasis obstruction and deficiency of spleen and kidney. Jiang *et al* [8] analysed the distribution of TCM symptom patterns in 475 in-patients with RA, finding that most of the occurrences were of damp-heat symptom pattern, which accounted for 41.7% of the cases. Le *et al* [9] retrospectively analysed the relationship between the TCM symptom pattern type and the immune index in 143 RA patients, showing that the anti-cyclic citrullinated peptide antibody and rheumatoid factor (RF) have the highest positive rate in damp-heat symptom pattern. Damp-heat symptom pattern predominates in the active stage of RA, and RA patients with damp-heat symptom pattern according to the standard were selected as the subjects of the study.

After years of study, our research team found that the Sanhuangyilong decoction displays a certain effectiveness in the treatment of RA with high activity by eliminating dampness.[10] This project aimed to investigate the effects of Sanhuangyilong decoction combined with MTX on TNF-α and IFN-γ, and the their role in the development of RA.