

Comparing Effectiveness of Western Protein-Based DMARDs and Traditional Chinese Therapies for Treatment of Rheumatoid Arthritis

Shixin Chu *

Shanghai High School International Division, Shanghai, China

* Corresponding Author Email: chu0308@powerbi.edu.kg

Abstract. Rheumatoid arthritis (RA) is a common autoimmune disease that causes complex immune responses. The pathogenesis of RA is complicated by the involvement of multiple cells, including innate and adaptive immune cells, making treatment difficult. Traditional Chinese medicine (TCM) and therapies differ from western protein-based drugs in the treatment of RA. When several Chinese herbals are normally used to treat RA in TCM, they are primarily targeted at some pro-inflammatory cytokines, such as interleukin 6 (IL-6) and interleukin 1 (IL-1). This project is investigating the mechanisms of several TCM and protein-based drugs. The effectiveness of traditional Chinese therapies such as acupuncture, tuina, and Chinese massages is also evaluated. Besides, the adverse effects and toxicity of researched drugs are listed, and the combination of Chinese medicines and modern pathologies are discussed, aiming to evaluate the effectiveness of TCM for treating RA using modern technologies and medical procedures.

Keywords: Rheumatoid Arthritis, TCM, DMARD, Protein-based Therapies.

1. Introduction

RA is an autoimmune disease that causes the immune system to attack healthy joint tissues. Females are more likely to show symptoms. Although there are no known causes of the disease, risk factors such as obesity, smoking, and genetics may increase the disease's likelihood.

The pathological mechanism of RA starts with the citrullination of collagen protein. Citrullination is the process of mutating the amino acid arginine and converting it to citrulline. This will result in trigger of the immune system. Antigen-presenting cells (APCs) then phagocytose the mutated collagen and present the specific antigen to the adaptive immune system through the MHC molecules on their membrane. This presenting process will trigger the activation of CD4⁺ T lymphocytes, which then causes the proliferation of specific synovial cells, secretion of pro- and anti-inflammatory cytokines, and stimulation of osteoclasts. These will all cause symptoms of RA.

No treatment could effectively cure RA. However, drugs that could relieve pain by nerve blocking or affect the immune system are widely used to mitigate the symptoms of RA.

“Huang Di Nei Jing,” which was one of the first TCM books, classified RA as “Bi” syndrome. “Bi” means obstruction in the human body by TCM studies. “Bi” is identified as the condition that there is not enough “qi” and blood in the human body, resulting from the invasion of coldness and dampness due to obstruction. According to TCM theory, RA symptoms are classified into the hot subtype and the cold subtype. Studies show that patients with hot symptoms have a higher level of anti-citrullinated protein antibodies (ACPA) in their bodies. ACPA could affect the auto-immune response negatively [1].

Several effective Chinese herbal medicines (CHM) were discovered a long time ago and documented in “Ben Cao Gang Mu,” a full encyclopedia of CHM written by Li, Shizhen in the 16th century. According to the book, an herb belonging to the Aconitum genus could effectively treat “Bi” syndrome and mitigate the symptoms of RA. There are recipes for CHM containing several different herbs that could also treat RA. For example, Xiangfanghuomingyin is an emulsion containing various herbs that could effectively treat RA.

Western protein-based therapies treating RA are often known as disease-modifying antirheumatic drugs (DMARDs). Various DMARDs operate in different mechanisms. DMARDs include TNF-

alpha inhibitors, IL-6 inhibitors, IL-1 inhibitors, inhibition antibodies, and T-cell targeted therapies. The difference between Chinese and western therapies for RA will be explained in this project.

2. Western medicine treatments and mechanisms

The vast majority of Western RA medications are classified as disease-modifying anti-rheumatic medications (DMARDs). Protein-based DMARDs are the most common. They are divided into two groups: conventional DMARDs and biological or antibody-based DMARDs. Leflunomide and sulfasalazine are two examples of conventional DMARDs. Leflunomide prevents lymphocyte proliferation by inhibiting pyrimidine synthesis. Sulfasalazine is an anti-inflammatory medication that prevents the release of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-alpha). Upregulation of pro-inflammatory cytokines, such as TNF-alpha, IL-6, and IL-1, is a significant factor in joint tissue damage, exacerbating symptoms. Biological DMARDs have various targets for inhibiting an overactive immune system and preventing an auto-immune response. Biological DMARDs such as abatacept and belimumab will be discussed in detail, as will their mechanisms. Most biological DMARDs are dosed by injection, while conventional synthetic DMARDs such as methotrexate and sulfasalazine are dosed orally in tablet forms. This is mainly because the structures of biological DMARDs like abatacept and belimumab are volatile. When dosed orally, stomach acids might denature the biological drugs, resulting in the drugs' malfunction [2].

2.1. IL-1 Inhibitors

IL-1 and IL-6 are pro-inflammatory cytokines that activate macrophages, stimulate fibroblast proliferation, and stimulate osteoclast production. These factors can cause RA pathological symptoms such as bone damage, cartilage breakdown, and the formation of synovial pannus. One of the most effective IL-1 inhibitor mechanisms is the use of interleukin-1 receptor antagonist (IL-1Ra) as an IL-1 inhibitor. IL-1Ra is a subtype of the IL-1 cytokine family that binds to IL-1 receptors to block the downstream intracellular pathway, as shown in Figure 1. One of its roles is to act as an anti-inflammatory therapy to prevent the adverse effects of IL-1. Anakinra is a prescription DMARD with mechanisms of inhibiting IL-1 cytokines. It is taken by injection. Adverse effects are being experimented with by giving patients the doses periodically for up to one month. The results show that there are no significant adverse effects. However, if anakinra is used with another DMARD with a different mechanism, the risk of severe infection will be higher than dosing Anakinra alone. The potential infections include influenza and urticarial lesions [3].

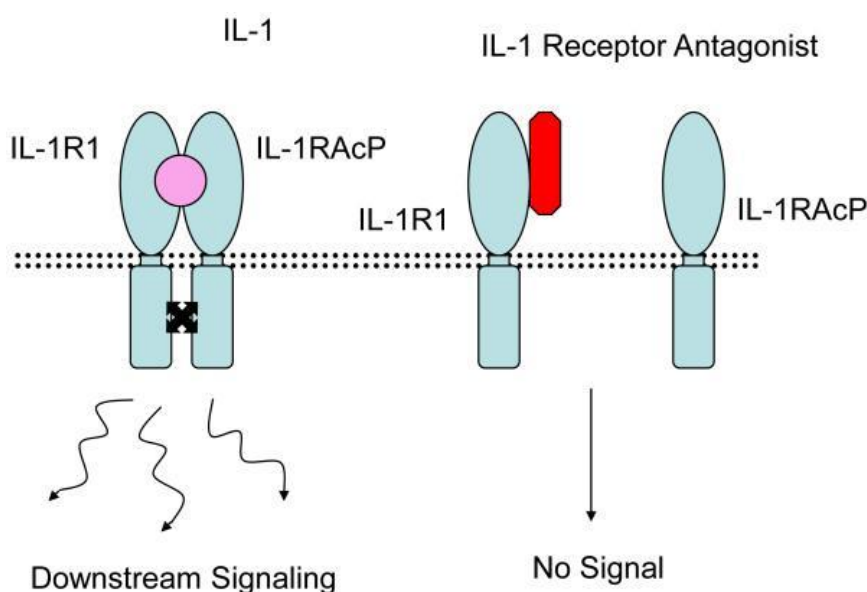


Figure 1. The schematic that IL-1Ra inhibits the IL-1 pathway [4]. The IL-1Ra, including anakinra, could bind to the IL-1 receptors to prevent the combination between IL-1 and IL-1 receptors.

2.2. Abatacept

Abatacept, also known as cytotoxic T lymphocyte-associated antigen-4 immunoglobulin fusion proteins (CTLA4-Ig), is a fusion protein that targets the T helper (Th) cell. It associates with antigen-presenting cells (APCs) such as macrophages or dendritic cells to selectively inhibit the activation of specific Th cells [5]. As Figure 2 shows, abatacept binds to CD80 and CD86 protein receptors on APCs containing the citrullinated collagen antigen. This will prevent CD80 and CD86 from binding to protein receptor CD28 on Th cells and activating them. This drug could potentially prevent the differentiation of Th cells and the production of plasma cells, downregulating the auto-immune response. Orencia is a prescription DMARD that uses abatacept for treatment. It is a clear and transparent solution with sterile water as a solvent, abatacept, and maltose and sodium chloride as solute. Each injection contains 250mg of abatacept. An adult patient weighing 60 to 100kg should take three injections or a 750mg daily dose. Adverse effects include the risk of infections and flu symptoms. Common infections include infection of the respiratory tract (1%) and bronchitis (0.7%). Extreme adverse effects include acute lymphocytic leukemia.

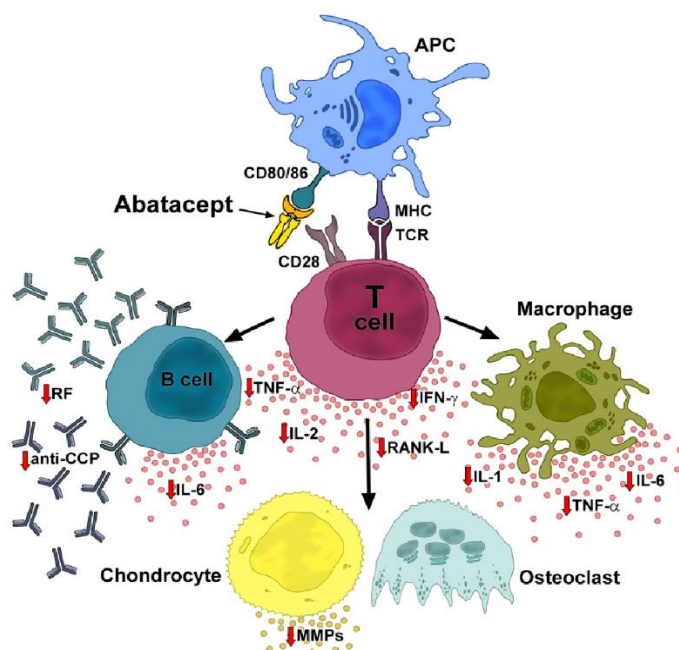


Figure 2. The schematic that abatacept inhibits activation of T cells [6]. Abatacept binds to CD80 and CD86 protein receptors on APCs to prevent the antigen-presenting process.

2.3. Belimumab

Belimumab is a human monoclonal antibody treatment that regulates B cells by interacting with B Lymphocyte stimulator protein (BLyS). It has the ability to prevent BLyS from binding to BLyS receptors. Many autoimmune diseases, including RA and Systemic Lupus Erythematosus, rely on BLyS. BLyS activates specific B cells, which may trigger an auto-immune response that results in hyperinflammation. Belimumab can alter the structure and function of BLyS after binding to it, preventing it from binding to B cell receptors such as BLyS receptor 3 (BR3) and blocking the following signal pathway, resulting in the reduction of hyperinflammation in joint cells, which causes RA symptoms [2][7].

3. Chinese treatments and mechanisms

The Chinese have a long history of treating RA. RA is classified as a "Bi" syndrome in traditional Chinese pathological theory. When elements such as wind, dampness, and cold attack the Yin and Yang, which represent the body's homeostasis, this is referred to as "Bi" syndrome. The weather and the environment are represented by the element dampness and coldness. For example, if the weather

is rainy and cold, these elements will enter the human body, causing RA symptoms. Acupuncture, CHM, and tuina (Chinese massage) are all effective RA treatments. CHM can be processed in two ways: as a water decoction or as capsules [8].

3.1. ALW

ALW is a perennial herb from China. Previous research shows that ALW could significantly increase the apoptosis rate of fibroblast-like synovial cells-rheumatoid arthritis cells (HFLS-RA). It could also regulate specific cytokines and gene expressions, such as TNF-alpha, IL-6, and toll-like receptor 4 (TLR4). In other words, this herb plays a vital role in inhibiting HFLS-RA cell proliferation and cytokine production, resulting in anti-rheumatic effects. Research also demonstrates that the processing approaches for ALW are significant for its effectiveness. The water-boiling processed product (submerging the drug into the water for one hour and boiling for 30 min) has much higher inhibition and apoptosis rates than organic monomer extraction products. (48.55% for inhibition rate and 14% for apoptosis rate in water-boiling products, 35.68% for inhibition rate, and 10% for apoptosis rate in WF-1 monomer component)

3.2. Xianfanghuomingyin

Xianfanghuomingyin is not a single herbal medicine like ALW but rather an herbal formula consisting of various herbal plants. Xianfanghuomingyin could block pro-inflammatory cytokine secretion and T-cell differentiation to treat RA. Studies show that interleukin 4 (IL-4) and GATA binding protein 3 (GATA-3) levels are being regulated to inhibit the activation and differentiation of CD3+ and CD4+ T cells. The drug also inhibits the activation of pro-inflammatory phenotypes of TH cells, Th1, and Th17. Similar to the mechanism of abatacept, it could act as a potential T-cell targeted treatment for RA [9].

3.3. Biqi capsule

Biqi capsule is a TCM that contains multiple herbs, including semen strychnine, pheretima, and radix changii. The herbs are ground into powder to be put into the capsule. The drug is identified as a synovial cell modulator that can prevent swelling of joint tissues due to cell proliferation or anti-inflammatory cytokines. A clinical study has been done to investigate Biqi capsule's effectiveness in treating RA. The results suggest that the Biqi capsule could be an effective drug for RA. The data shows that 81.2% of the patients who received Biqi treatment achieved a 20% decrease in the number of swollen joints compared to 81.5% of the patients for the positive control leflunomide group. However, the fraction of patients who reported adverse effects in the Biqi group is significantly less than that of leflunomide, with 11.4% for Biqi and 40% for positive control. All negative effect for Biqi is the increased secretion of liver enzymes in the body [8].

3.4. Tuina and acupuncture

Tuina, or traditional Chinese massage, could relax muscles and the nervous system to mitigate pains in the human body. However, Tuina could be an adjuvant therapy method for RA. Tuina could be used as a placebo for patients with RA. After Tuina, patients usually feel relieved.

Acupuncture is the practice of inserting thin needles into specific points, called "Xue," in the human body. In the theory of traditional Chinese medicine, when activation of the "Xue" in the human body, the internal "qi" could flow smoothly in the body to maintain homeostasis. To explain the mechanism for acupuncture in modern pathology, acupuncture can regulate the production of inflammatory cytokines and release stress. Multiple studies reveal that level of cytokines TNF-alpha has been reduced after acupuncture and that several anti-inflammatory cytokines, including interleukin 2 (IL-2) and interleukin 4 (IL-4), are upregulated after the treatment [10].

4. Conclusion

It can be concluded that both western DMARDs and TCM treatments for RA have their negatives and positives. Generally, western protein-based drugs have more significant adverse effects than TCM herbal therapies. Protein-based DMARDs may have a chance of causing serious upper respiratory tract infections and even leukemia for the worst. For TCM herbal therapies, serious adverse effects occur significantly less frequently than for protein-based DMARDs. Though few herbal recipes often contain a small number of toxic elements if ingested in emulsion form.

The major disadvantage of TCM treatment is that it often lacks mechanisms supported by pathological theories. TCM herbal recipes are created based on experience and attempts. Thus, there is usually no clear explanation of how various TCM therapies work in our bodies for RA treatment. However, this problem can be fixed with the use of modern medical technologies.

Computational modulation techniques could be used to discover new TCM RA therapies and make them more personalized and effective. Models could be created to suggest new recipes for herbal drugs targeting a different type of RA. For example, a patient with “hot” symptoms will have a different treatment than a patient with “cold” symptoms since the difference in symptoms is caused by different factors. RA is a very complex disease that multiple factors could cause. Furthermore, more clinical trials for TCM should be done to eliminate less effective TCM therapies and to keep advancing potential TCM drugs.

Combining TCM with western protein-based DMARDs to treat RA is also important in modern medicine. Thus, more research should be done on TCM DMARDs and protein-based DMARDs.

References

- [1] Zhang P, Li J, Han Y, et al. Traditional Chinese medicine in the treatment of rheumatoid arthritis: a general review[J]. *Rheumatology International*, 2010, 30(6): 713-718.
- [2] Guo Q, Wang Y, Xu D, et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies[J]. *Bone research*, 2018, 6(1): 1-14.
- [3] Gabay C, Arend W P. Treatment of rheumatoid arthritis with IL-1 inhibitors[C]. *Springer seminars in immunopathology*. Springer-Verlag, 1998, 20(1): 229-246.
- [4] Henderson C, Goldbach-Mansky R. Monogenic IL-1 mediated autoinflammatory and immunodeficiency syndromes: finding the right balance in response to danger signals[J]. *Clinical immunology*, 2010, 135(2): 210-222.
- [5] Herrero-Beaumont G, Calatrava M J M, Castañeda S. Abatacept mechanism of action: concordance with its clinical profile[J]. *Reumatología Clínica (English Edition)*, 2012, 8(2): 78-83.
- [6] von Kempis J, Dudler J, Hasler P, et al. Use of abatacept in rheumatoid arthritis[J]. *Swiss medical weekly*, 2012, 142.
- [7] Blair H A, Duggan S T. Belimumab: a review in systemic lupus erythematosus[J]. *Drugs*, 2018, 78(3): 355-366.
- [8] Pan H D, Xiao Y, Wang W Y, et al. Traditional Chinese medicine as a treatment for rheumatoid arthritis: from empirical practice to evidence-based therapy[J]. *Engineering*, 2019, 5(5): 895-906.
- [9] Li T, Zhang A, Miao J, et al. Applications and potential mechanisms of herbal medicines for rheumatoid arthritis treatment: a systematic review[J]. *RSC advances*, 2019, 9(45): 26381-26392.
- [10] Xing Q, Fu L, Yu Z, et al. Efficacy and safety of integrated traditional Chinese medicine and Western medicine on the treatment of rheumatoid arthritis: a meta-analysis[J]. *Evidence-based Complementary and Alternative Medicine*, 2020, 2020.