

Investigation of Early Diagnosis and Treatment for Rheumatoid Arthritis

Jiayong Zhang *

International department, Beijing 101 Middle School, Beijing, China

* Corresponding author: 24john.zhang@beijing101id.com

Abstract. Rheumatoid arthritis (RA) is a typical chronic autoimmune disease. Beyond 1.5 million patients are affected by this disease. Early diagnosis and treatment are crucial for RA patients. Several golden standards and tools including ultrasonography are primarily applied in the RA clinical detection. Levels of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) indicate the occurrence and progress of this disease. Inflammation is involved in the progress of RA pathogenically even though the specific cause is still under learning. T lymphocytes and B lymphocytes are activated to regulate the immune responses in the disorder. As a results, disease-modifying anti-rheumatic drugs (DMARDs) are under investigation to inhibit the increase of RA-relevant lymphocytes. Methotrexate and leflunomide (LEF) are the two most frequently applied DMARDs in this chronic disorder. When monotherapy shows low efficiency, triple therapy could be used to improve the treatment. This article briefly introduced about the definition, mechanism, and treatments of the RA.

Keywords: Rheumatoid Arthritis, Early Diagnosis, Inflammation.

1. Introduction

RA is an autoimmune disease that frequently influences synovial joints. Rheumatoid arthritis causes severe pain and functional limitations, causing endless suffering to patients; RA is characterized by inflammatory and degenerative changes in various joint structures, hyperplasia of articular cartilage and synovial membranes, destruction of the compressed cartilage portions between joints, progressive stiffness and deformity. in 2005, it was estimated that 1.5 million people, or 0.6% of adults over the age of 18, were affected by RA in the United States, and in recent years, with the number of patients increasing across gender and age groups; RA leads to shorter working hours and earlier retirement than other forms of arthritis, and patients are said to have three times higher household income [1]. In some western countries, the probability of becoming a patient with RA is about 0.5-1.1%, with an annual increase of 0.25% [1]. It is widely distributed in the Americas. RA occurs more frequently in female. Multiple studies have shown the prevalence increases with years. Functional deterioration with progressive disability is the most common factor in patients with RA who are initially treated with aspirin and other nonsteroidal anti-inflammatory drugs. As RA progressed, DMARDs were introduced. Multiple DMARDs therapy is only offered to patients with severe disease. Remission with minimal radiological damage and without functional deterioration is a key need for RA treatment. Over the past 50 years, relevant drugs, diagnostic tools and disease management strategies have been largely developed. This project will discuss advances in elucidating the etiology and developing diagnostic and treatment strategies.

2. Pathophysiology of RA

2.1. Risk factors in RA

Although researchers have not yet discovered the specific cause of RA, evidence suggests that this autoimmune disease is the result of the coordinated action of several risk factors [2]. It increases with age. RA has the highest incidence in adults in their 60s. RA occurs more frequently in female.

Genetics may play a role in RA. Studies have shown that human leukemia antigen (HLA) type II aggravates arthritis. Certain populations may also have a predisposition to RA. For example, people

who have experienced radiation or childbirth are at higher possibility to get RA, while nursing female have been found to be less insensitive to RA. In addition to these causes, other research provided evidence that smoking and smoke exposure are involved in a higher risk of developing RA and more serious diseases. RA is caused by a disorder of the sweat glands, and a new theory suggests that one of the possible causes of RA may be inadequate sweating [2].

2.2. Inflammation in RA

Understanding the pathogenic role of inflammation in RA could improve the development of therapy strategies. Various cytokines can activate osteoclasts that start making proteases and collagenases that erode the joints, while anti-inflammatory cytokines fail to suppress the inflammation. Specifically, it starts with genetic factors. Mutations in type II collagen led to guanylation, where arginine becomes guanine [3]. Antigen-presenting cells (APCs), which are typically dendritic cells (DCs) in this process, then recognize the citrullinated protein as a foreign substrate and engulf the collagen due to an abnormality in the HLA-DR gene [3]. In addition, specific antigens of variant proteins can be presented by APCs and recruit CD4⁺ helper T (Th) cells in lymph nodes. Upon Th cell activation, multiple cytokines are produced to regulate the differentiation of Th subpopulations. Th cells have multiple functions and secrete. They are classified according to cytokines: Th1-type cells produce certain cytokines, which accelerate the local inflammation [3][4]. Type 2 Th (Th2) cells are stimulated by IL-2 and produce anti-inflammatory [4]. Th2 cells also regulate B cells and convert immunoglobulins (Ig) to IgE. ACPA occur as a result of abnormal antibody responses to various citrullinated proteins. During maturation, ACPA production reflects disruption of immune tolerance and Th cells stimulate B cells to produce more ACPA [4].

3. Early diagnosis of RA

The symptoms of this disorder are diverse and nonspecific, with some patients complaining of wrist pain and others experiencing inflammation in the knee joints. However, many people do not understand the disease and tend to think that "joint pain" is a natural consequence of aging; in 1987, the American College of Rheumatology developed seven criteria to identify patients with RA, including morning stiffness for a long time, pain in multiple joints, pain in the joint pain in the hands, symmetrical swelling and rheumatoid nodules [5].

To diagnose RA, at least 4 of the listed symptoms must be present and 1-4 symptoms must persist for at least 6 weeks [6]. In the clinical diagnosis of RA, medical history is necessary to be reviewed and several visits are needed to exclude similar autoimmune disease. Besides the measurement of level of RF and APAC, ultrasonography and computed tomography imaging are also primary served as the detection tool to image the patients' bony pathology [6].

Patients with RA experience pain, stiffness, and limited joint movement. Many become unable to perform certain activities and become depressed. In addition, motivation for these activities is reduced. Another important factor that accelerates joint deterioration is that many people believe that painkillers are the only treatment because of the limited knowledge related to this disorder. With the development of RA, the financial influences are impressed and further highlight the significance of the RA early diagnosis.

4. DMARDs

DMARDs refer to a series of drugs to mitigate the progression of RA. The common mechanism of DMARDs to treat RA is to target the inflammation responses in patient's body [7]. As a result, it could need takes several weeks to eases the symptoms associated with RA [8].

Methotrexate was served as a chemistry medicine to treat cancer at the first and the structure of this DMARD refers to Figure 1. However, it was then identified as a core therapeutic agent in the treatment of RA in smaller dose. Methotrexate is recommended as the first DMARD for most RA patients. It

refers to a chemical substrate with a similar structure to folic acid. This kind of medicine aims to influence various proteins in crucial metabolism pathways and upregulate the adenosines production to cause dysfunctional DNA anabolism [8]. Through this process, the pro-inflammatory cytokines and immune cells could be downregulated. However, the exact process that methotrexate treats RA is still under learning.

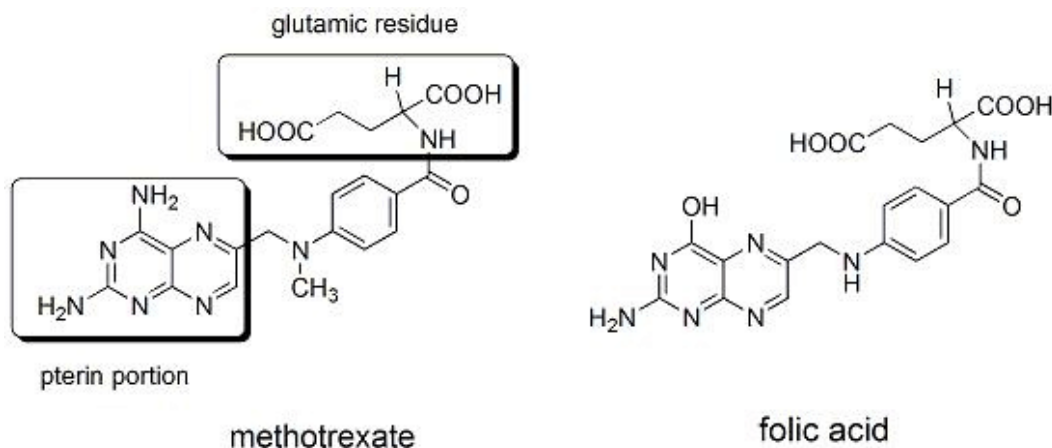


Figure 1. The chemical structure of methotrexate and folic acid [9].

Another DMARD, LEF is the latest DMARD to be introduced and is critical to slow the progression of RA. The structure of LEF refers to Figure 2. LEF could be used alone or applied in polytherapy for RA through oral route [7]. Similar to methotrexate, dihydroorotate dehydrogenase could be targeted by LEF to cause impair DNA formation. In this way, the proliferation of lymphocytes and other critical immune cells could be downregulated by LEF, leading to the mitigation of RA [7]. So, LEF is most served as the alternative medicine for those patients who are insensitive to methotrexate. The diagnosis of patients' blood cell levels and hepatotoxicity is necessary even though methotrexate and LEF are characterized by low toxicity. Several adverse effects are involved in these two RA DMARD treatments, including canker sores and dyspepsia [7]. Folic acid is required for the patients under the therapy of methotrexate to mitigate specific adverse effects. Methotrexate and LEF are prohibited to be used for gravid females with RA due to the teratogenic effects.

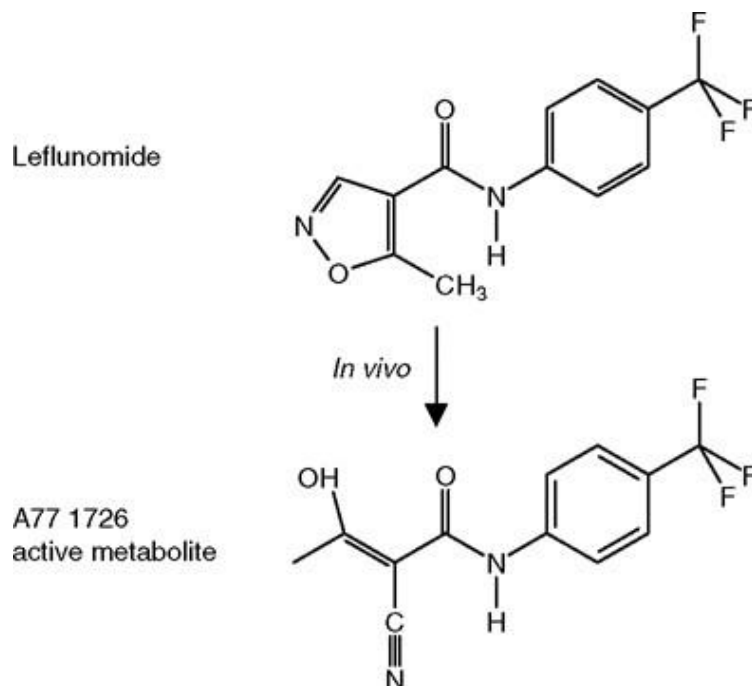


Figure 2. The schematic of structure of LEF and its active state [10].

Monotherapy of methotrexate or LEF is mainly used to treat RA patients at the early stage. In the cases with insufficient monotherapy, triple therapy is proposed in recent research. The combination of methotrexate, sulfasalazine and hydroxychloroquine is typically used because of the low price and promised safety. Previous studies pointed out that the synergy of these three DMARDs could provide more efficient curative effects for RA with a lower risk of unfavorable effects compared to one DMARD therapy strategy. However, the clinical uses of triple therapy for RA are still controversial because of the limited data and complicated cases.

5. Conclusions

In this project, the global effect, pathogenesis, and treatments of RA were discussed. As a global affecting autoimmune disease, RA influenced more than 1.5 million people's daily life. Nowadays, RA still has a 0.25% of increase rate annually, causing more people to suffer from this life-long disaster. Early diagnosis of RA is highly significant to improve outcomes. Several golden standards were identified for the detection of RA bony pathology. Besides, ultrasonography and computed tomography imaging are also primary served. Genetic risk factors are associated with it. The typical examples are the mutations of HLA and its alleles. A series of inflammation responses also play a pathogenic role in this disease. Rheumatoid factors and citrullinated proteins are recognized by various immune cells. Specifically, certain non-specific immune cells can further recruit related lymphocytes to attend to the pathogenic process. Among them, Th cells can secrete regulatory cytokines to activate downstream pathways, when B lymphocytes are mainly associated with ACPA to accelerate RA. In the past, the relief of related symptoms are the primary object of RA therapy strategies. With the increasing understanding of RA pathogenic mechanisms, DMARDs are proposed as the current common treatments which aim to prohibit the development of RA. Methotrexate and LEF are two most frequently used DMARDs in this chronic disorder. They showed high efficiency in approximately 35 percent of patients by inhibiting the proliferation of RA-relevant lymphocytes while multiple unfavorable effects could happen within the therapy period. Various combinations of DMARDs are also evaluated in previous studies. Triple therapy showed efficient curative effects for RA with a lower risk of unfavorable effects compared to one DMARD therapy strategy, especially for the combination of methotrexate, sulfasalazine, and hydroxychloroquine. However, more evidence that supports the effectiveness of the triple therapy is still expected due to some controversial results.

References

- [1] Littlejohn E A, Monrad S U. Early diagnosis and treatment of rheumatoid arthritis [J]. Primary Care: Clinics in Office Practice, 2018, 45 (2): 237 - 255.
- [2] Aletaha D, Smolen J S. Diagnosis and management of rheumatoid arthritis: a review [J]. Jama, 2018, 320 (13): 1360 - 1372.
- [3] Groh V, Brühl A, El-Gabalawy H, et al. Stimulation of T cell autoreactivity by anomalous expression of NKG2D and its MIC ligands in rheumatoid arthritis[J]. Proceedings of the National Academy of Sciences, 2003, 100 (16): 9452 - 9457.
- [4] Nigrovic P A, Binstadt B A, Monach P A, et al. Mast cells contribute to initiation of autoantibody-mediated arthritis via IL-1 [J]. Proceedings of the National Academy of Sciences, 2007, 104 (7): 2325 - 2330.
- [5] Klarenbeek N B, Kerstens P J S M, Huizinga T W J, et al. Recent advances in the management of rheumatoid arthritis [J]. bmj, 2010, 341.
- [6] Radu A F, Bungau S G. Management of rheumatoid arthritis: an overview [J]. Cells, 2021, 10 (11): 2857.
- [7] Grijalva C G, Chung C P, Arbogast P G, et al. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis [J]. Medical care, 2007: S66 - S76.

- [8] Yap H Y, Tee S Z Y, Wong M M T, et al. Pathogenic role of immune cells in rheumatoid arthritis: implications in clinical treatment and biomarker development[J]. Cells, 2018, 7 (10): 161.
- [9] Ma L, Wang C, He Z, et al. Peptide-drug conjugate: a novel drug design approach [J]. Current medicinal chemistry, 2017, 24 (31): 3373 - 3396.
- [10] Rozman B. Clinical pharmacokinetics of leflunomide[J]. Clinical pharmacokinetics, 2002, 41 (6): 421 - 430.