Dean&Francis

ISSN 2959-409X

MS003712

Overview of Rheumatoid Arthritis: Symptoms, Causes, and Treatments

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Abstract:

Rheumatoid arthritis (RA) is a long-term disease with the characteristics of inflammation throughout the body. Patients with RA typically experience joint pain and other complications. The pathogenesis of RA is complicated, with the factors of genes, environment, and auto-antibodies. Rheumatoid arthritis can lead to more serious consequences in the other parts of the body without treatments. Hence, the drugs for the treatment of RA are necessary. Nowadays, there are four main types of drugs: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and biological agents. This article will mainly discuss the pathogenesis of RA and compare two types of drugs, NSAIDs, and DMARDs, with one selected for each.

Keywords: Rheumatoid Arthritis, RA, Pathogenesis of RA, Treatments, Disease-modifying Antirheumatic Drugs, DMARDs, methotrexate, Non-steroidal Anti-inflammatory Drugs, NSAIDs, naproxen, structure, functions

1 Introduction

Rheumatoid arthritis (RA) is an auto-immune disease in the system with long-term inflammation. It can lead to some main symptoms in clinical treatment, such as cartilage destruction, pannus formation, and synovial proliferation [1,2]. RA can happen in any joint in the body but usually influences the metacarpal bone and metatarsophalangeal joints around the wrists and knees. According to observation, RA often happens on wrists in most patients, and tenderness usually happens in their elbows and knees, as shown in Fig.1 (left), while swelling normally occurs in patients' small joints such as the metacarpophalangeal joint [3]. As a chronic inflammatory disease, RA can ultimately lead to joint deformities and loss of function, as shown in Fig.1 (right) [4].

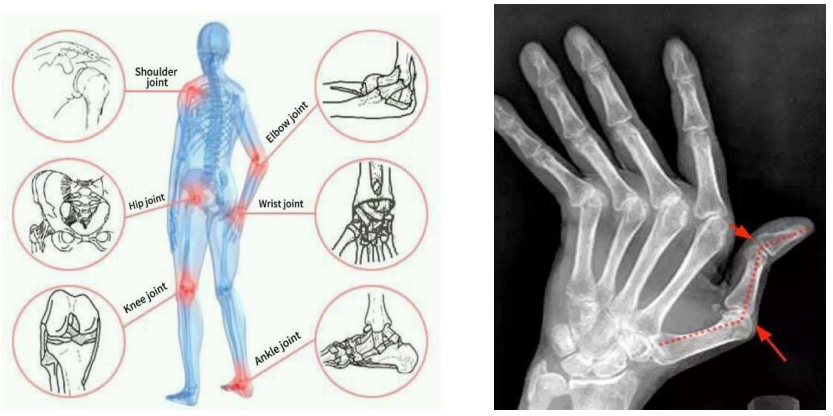

Fig.1 Large joints that usually happen with RA (left). Joint deformities (right).

Additionally, RA can cause several complications, such as cardiovascular, lung disease, sleep disorder, and Felty syndrome [5]. According to analysing data from the Global Burden of Disease, RA usually happens in patients aged between 65 to 69 and the incidence in women is higher than in men, with a ratio of 3:1 [1,6]. The treatment aims to lower the feelings of pain, improve symptoms and also, prevent the occurrence of complications. To achieve this goal and prevent permanent injury, RA needs to be diagnosed and treated as soon as possible [1]. Hence, understanding the pathogenesis of RA and the therapeutic principle of typical drugs is important and necessary.

2 Diagnosis and Pathogenesis of RA

2.1 Four Criteria of Diagnosis

Four criteria, which are affected joint number, RF and ACPA tests, phase reactants, and symptoms duration, released in 2010 show a systematic diagnosis of RA, as shown in Fig. 2 [7,8].

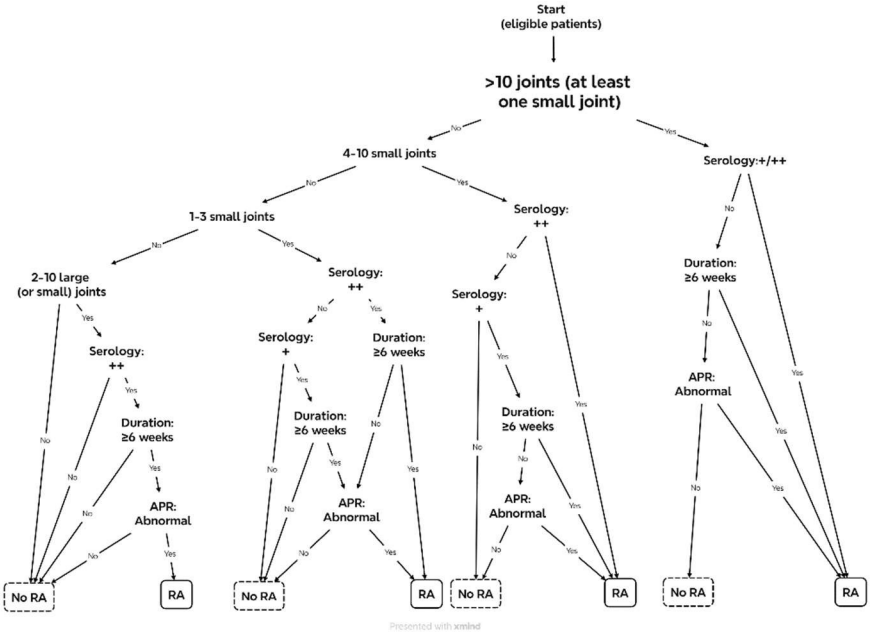

Fig. 2 The systematic diagnosis process of RA. APR means the response of the acute phase. Serology: one positive (+) sign means the low-positive status of (RF) or anti-citrullinated protein antibody (ACPA) and two positive (++) signs mean high-positive status [7,8].

In addition to synovial fluid, synovium, and other complications, two types of antibodies, RF and ACPA, anti-citrullinated protein antibodies, had been noticed in the clinical diagnosis of RA [4,5]. Even though RA can happen without the test of RF, the presence of RF in the blood can still be an important way to help identify the disease. In clinical practice, the presence of RF can be found in approximately 80% of patients with RA and they get pos-

ISSN 2959-409X

itive results in the RF test [5,9]. It shows that with these antibodies, the immune system starts to attack its tissues, which may ultimately cause inflammation and damage joints or other organs [9]. The positive result of the ACPA test indicates the higher severity of the phenotype of RA and the increase of mortality and ACPA can be tested about 10 years before the typical symptoms occur in the clinical practice [4].

2.2 Pathogenesis

In most autoimmune diseases, clinical heterogeneity, polygenicity, and the contributions of multifactor, which typically include the factors of gene and environment, are shown in the clinical basis [10]. T-cells are cytotoxic and auto-reactive and will affect all the cases of autoimmune diseases [4,10].

2.2.1 Auto-antibodies

Some kinds of auto-antibodies can be tested in RA patients and the most common auto-antibodies studied are RF and ACPA. RF, formed from B-cells clustered in lymphoid follicles and germinal structures in the inflamed RA synovium is the auto-antibody targeting the Fc-portion of IgG and was discovered approximately 70 years ago [11-13]. Generally speaking, the immune complex formed by RF and IgG may initially generate a rapid antigen clearance mechanism. However, RF is considered without its' function of protection because of the different mechanisms compared with other conditions. Hence, even though RF tests can be one of the characteristics of RA, the clinical practice indicates not all patients with RA have positive results in RF tests. ACPA is also a type of auto-antibodies and usually presents with RF at the same time. However, compared with RF, ACPA has a higher level of sensitivity and specificity and will affect inflammation and mortality more. ACPA plays a more important role and has a good value in the diagnosis of RA [4,11,12]. The presence of RF and ACPA can increase joint inflammation by interacting with each other and they can also activate the production of macrophages and cytokine [4,14].

2.2.2 Genetic Factors

Regarding genetics, the major histocompatibility complex (MHC) is significant in most autoimmune diseases, especially in RA [3,10]. HLA-DRB1 in HLA class II antigens is the most important in the pathogenesis of RA. HLA-DRB1*01 and HLA-DRB1*04 contain a 'shared-epitope' sequence, which presents the antigen to T lymphocytes [3,15].

2.2.3 Environmental Factors

The research shows that smoking is the most common risk factor and the positive result of serology is associated with smoking for a long time [3]. In addition, occupational and infectious factors can also cause RA. The job environments can include long-time exposure to heavy metals and solvents and the infections are affected by viruses or bacteria [4]. Fig.3 below shows the factors that may cause RA [16].

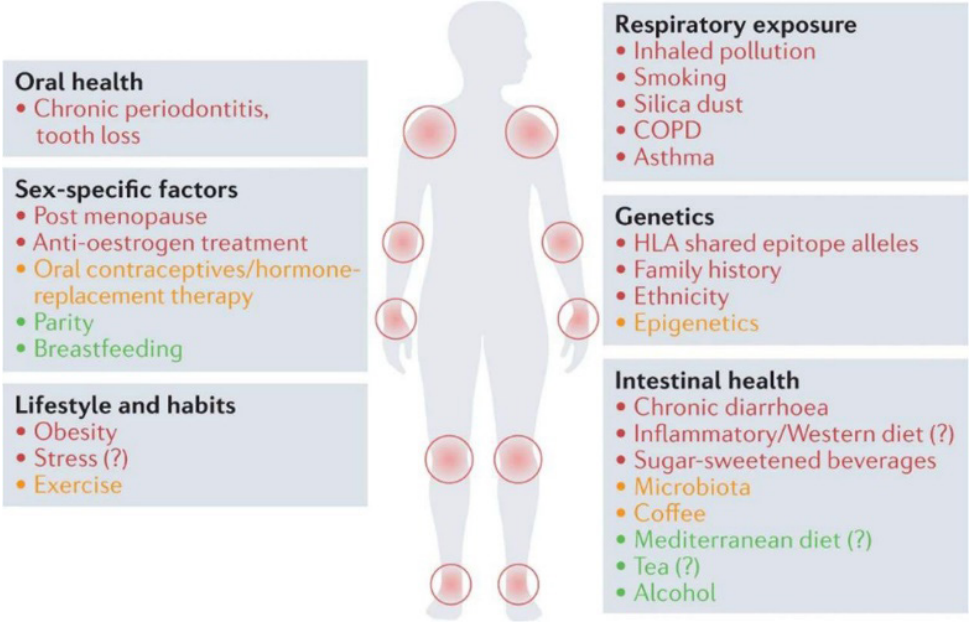

Fig.3 Factors that may cause RA. Text in Green: protective factors; Orange text: weak evidence; Red text: detrimental factors [16].

3 Treatment for RA

Even though RA is a permanent disease and there is no specific drug for the treatment of RA, several medical approaches are used to help control and improve RA [4,15]. There are mainly four main types of drugs that can be used: disease-modified anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and biological agents [4]. In this paper, DMARDs and NSAIDs are introduced and the specific drugs, methotrexate and naproxen, are mainly discussed and compared.

4 Disease-modifying Antirheumatic Drugs (DMARDs)

DMARDs are very often used in the treatment of RA, and they play the most important role nowadays. The ability of DMARDs is that can improve and delay RA progression. In DMARD, methotrexate is the most important one and has been widely used for more than fifty years [15,17].

4.1 The Background of Methotrexate (MTX)

Methotrexate (MTX) is also called amethopterin. MTX is the derivative of folic acid and it can disrupt the metabolism of the folic acids. In the beginning, methotrexate was developed as an anticancer agent and treated for cancer, but now it can be used to treat many kinds of diseases, like RA, juvenile rheumatoid arthritis (JRA), psoriasis and so on [18].

4.2 The Structure of MTX

The chemical formula of methotrexate is C20H22N8O5. The structure of MTX is shown in Fig.4.

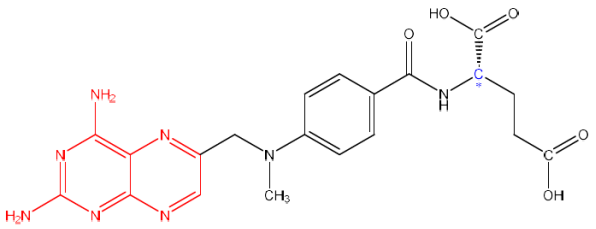

Fig.4 The chemical structure of MTX.

To consider the structure of MTX, the right-hand side carbon chain containing two carboxylic acids is similar to glutamic acid in structure. The carbon labelled in blue is a chiral centre with a S configuration. The red part in the figure above is a diaminopteridine ring system which can connect to its binding site, as shown in Fig.5 [19].

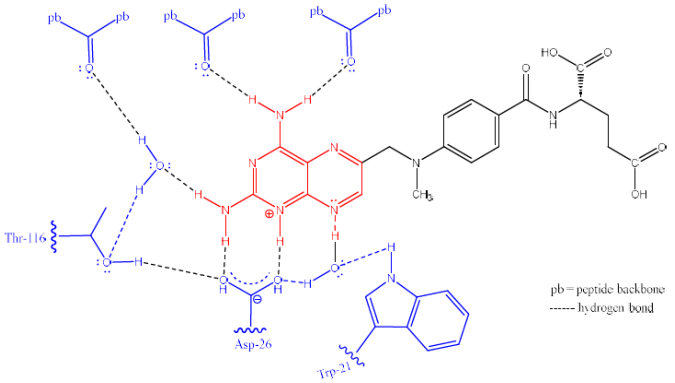

Fig. 5 Binding interactions for diaminopteridine ring and its binding site.

4.3 Formulations of MTX

To discuss whether MTX can be orally absorbed, Lipinski's rule of five is the most important rule to consider. In the rule, it states that orally absorbed drugs tend to obey four factors. MTX obey the two rules which are molecular weight no more than 500 $gmol^{-1}$ and the value of LogP no more than 5. However, the other two rules, hydrogen bond donors (HBD) and acceptors (HBA) no more than 5 and 10, respectively, are not satisfied by MTX [20]. Fig. 6 shows that the number of HBD and HBA.

ISSN 2959-409X

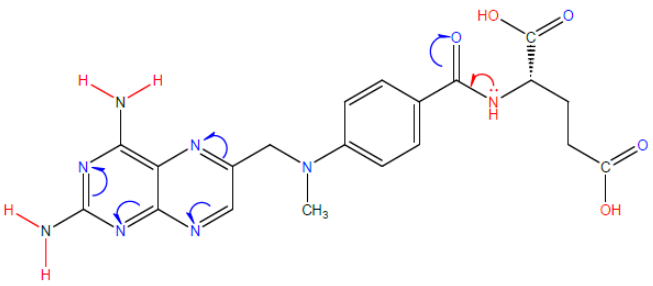

Fig. 6 The HBD (red) and HBA (blue) in methotrexate.

Even though MTX does not obey the rule, it can still be an oral medicine to take. Methotrexate can also be used in injections including intramuscular injection, subcutaneous injection, intra-arterial infusion, intravenous infusion, and intrathecal injection [17].

4.4 Mechanisms of MTX

4.4.1 Folate Antagonism

The first mechanism of methotrexate is folate antagonism. The ability of MTX that makes it important is the inhibition of the enzymes that catalyse the formation of purines and pyrimidines so that MTX can prevent the reproduction of malignant cells. As an antifolate agent, MTX can block the dihydrofolate reductase, which is usually called DHFR [17,18]. DHFR is a common enzyme that can catalyse the transformation from dihydrofolate to tetrahydrofolate with the consumption of NADPH [21]. MTX can inhibit the folates in the cells to reduce the purines and pyrimidines. Hence, it is unsurprising that it can be applied to inflammatory diseases [18].

4.4.2 Influence of Adenosine

In addition, MTX can also affect the adenosine in its mechanism and this opinion has been recognised for several years. Adenosine is a mediator with the ability of anti-inflammation, and it can block the enzyme called 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (ATIC), which is used for the synthesis of purine and change of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) to formyl AICAR. Because of the inhibition of ATIC, AICAR and its metabolites increase so that they can block the enzymes that participate in the decomposition of adenosine and adenosine monophosphate (AMP). However, there is a limitation and variation between the interaction of MTX and adenosine nowadays. Hence, there is no exact rule of the mechanism, and this is still an interesting topic to study [3,17,18].

4.4.3 Inhibition of Polyamines

Through blocking DHFR, MTX can reduce the tetrahydrofolate and methyltetrahydrofolate (5-CH3-THF) that can help to produce polyamines. The production of polyamines will decrease because of the mechanism that can decrease methylation. However, inhibiting the polyamine is not the most essential mechanism due to the less likely to show the effect of MTX in RA [22].

4.5 Side Effects and Toxicity

Many people consider the side effects of using the MTX. Several side effects have happened before, including the influences on livers, gastrointestinal systems, lymphatic systems, respiratory systems etc. Many patients who use MTX for the treatment of RA suffer from the impacts on gastrointestinal systems, which are the most frequent organs affected by the MTX [23].

Even though high-dose MTX (usually a dosage higher than 500 mg/m^2) is safe for most patients, it still has significant toxicities. It risks causing worse results, including mortality in accidents or a worse anticancer result. Hence the use of MTX for patients should be monitored and administrated well by the governments and hospitals [24].

5 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The main function of NSAID is not for the therapeutic purpose, NSAIDs are used to relieve pain and inflammation [3,4]. NSAIDs exert their effects by inhibiting cyclooxygenase (COX), which is an enzyme that participates in the transformation from arachidonic acid to prostaglandins (PGs). As shown in Fig. 7, the two types of NSAIDs are treated for different COX enzymes [25].

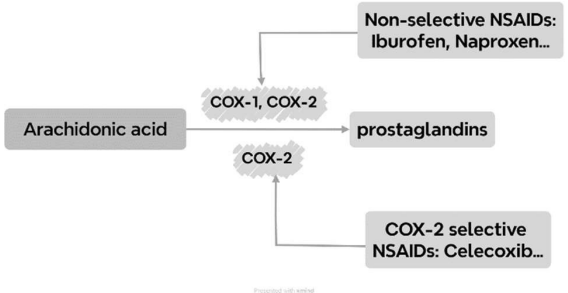

Fig. 7 Two types of NSAIDs that are treated for different COX enzymes.

NSAIDs are catalogued through their chemical structures: propionic acids, indoleacetic acids, phenylacetic acids, and so on. Non-selective inhibitors are the most commonly used in the treatment of RA. However, the safety problems are more concerned with the use of NSAIDs to treat RA now. Instead of aspirin, ibuprofen and naproxen are safer to be used [3,26,27]. In the paper below, naproxen as a specific example will be introduced and discussed in detail.

5.1 The Introduction of Naproxen

Naproxen was studied in the 1970s and it is a non-selective inhibitor that aims to enzymes, COX-1 and COX-2 [28].

To consider the structure of naproxen, the chemical formula of naproxen is C14H14O3. The structure of naproxen is shown in Fig. 8. The carbon with red labelled is a chiral centre with S configuration. The S configuration of naproxen is much more active than the R configuration [27].

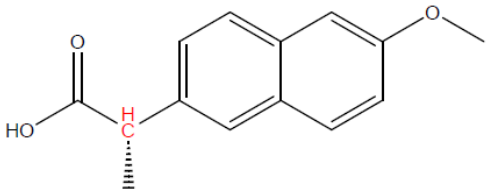

Fig. 8 The chemical structure of naproxen.

5.3 The Formulation of Naproxen

According to Lipinski's rule of five, good oral medicines need to obey four rules, which are molecular weight no more than 500 $gmol^{-1}$, the value of LogP no more than 5, HBD no more than 5 and HBA no more than 10 [20].

The molecular weight is 230.259 $gmol^{-1}$ and the LogP value of naproxen is 3.3. As shown in Fig. 9, the number of HBD of naproxen is 1 and the number of HBA is 3. These data show that naproxen can be used orally. In 2–4 hours after taking naproxen, it can show the maximum effect [28].

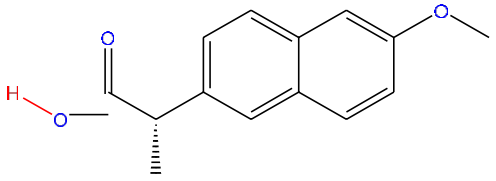

Fig. 9 The HBD (red) and HBA (blue) in naproxen

5.4 Mechanisms of Naproxen

5.4.1 Inhibition of Cyclooxygenase (COX)

In the mechanism of naproxen, the two subtypes of COX enzyme, COX-1 and COX-2, are inhibited by naproxen. COX-1 has an important effect on constitutive expression in the maintenance of the barrier in the gastrointestinal mucosa, while COX-2 is mainly used for inducible inflammation and pain [26,30].

The inhibition of COX can affect PG production, especially PGD2, PGE2, PGF2a and PGI2. Hence, inflammation and the feeling of pain can be relieved to a certain extent [25]. The anti-inflammation effect of naproxen inhibits the production of COX-1 and COX-2, reducing the generation of PGs. Because of the inducible effect of COX-2, the inhibition of COX-2 can help more to reduce the inflammation. However, at the same time, COX-1 is also represented in RA and other joint diseases, especially in synovial lining [31].

5.4.2 Influence on the Change of Polyamines

There is a possibility that naproxen can influence the polyamines that are necessary for the growth of cells. The growth of polyamines has been proven to cause malignant growth so polyamines can be the new target for the treatment of RA [30,32]. There is an experiment that has proven that naproxen can lead to the change of polyamines at the mRNA level and the most significant one is because of the rise of SSAT and SMOX expression [30]. This suggests that naproxen may affect RA through the change of polyamines.

5.5 Side Effects and Toxicity

The use of NSAIDs is now concerned about its side ef-

ISSN 2959-409X

fects. Naproxen and other NSAIDs may cause renal insufficiency, insomnia, gastrointestinal (GI) bleeding and a high risk of cardiovascular diseases [26]. In the treatment of RA, naproxen is usually used in the long term to relieve pain and inflammation. Hence, many people worry about the side effects and toxicity of naproxen. Usually, the use of naproxen is administrated and before the usage, patients need to be asked about their organs. The normal dose for the treatment of RA is between 220 and 550 mg per half day and patients with discomfort with GI need to take it with meals [26,31].

6 Discussion between MTX and Naproxen

MTX and naproxen are used in treating RA with different functions. MTX is used primarily to improve the disease, and naproxen aims to alleviate the pain. Both MTX and naproxen have the S configuration in their structure. According to the formulation, naproxen is fully satisfied with Lipinski's rule and can be taken orally, while methotrexate can be used in the mouth or by injection. Both two drugs are used as inhibitors in their mechanisms. They can influence polyamines but may be in different ways. However, the effect of polyamines is not the main mechanism of the two drugs. They have the specific mechanism for the treatment of RA.

Considering the side effects and dosages, methotrexate needs to be controlled in the low dosage for most patients, below 500mg. In comparison, naproxen ranges from 220 to 550 mg depending on the extent of the disease. However, naproxen cannot be taken in the long term because of the risks of adverse effects and burden.

7 Conclusion

RA is a common disease in middle-aged people and happens more often in women. According to the three main pathogenesis of RA, only the environmental factor can be controlled. The pathogenesis of RA is still a big topic to study. The treatments of RA may need to be improved with fewer adverse effects and toxicity. Nowadays, biological agents are developed gradually and the mechanism will be studied continuously. Because of the complexity of RA, the patients need to be examined more carefully according to the criteria of RA to avoid misdiagnosing and receive the treatments as fast as possible.

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