

Rheumatoid Arthritis: Current Treatments and Future Outlook

Li You *

Suzhou Foreign Language School, Suzhou, 215000, China

* Corresponding Author Email: 1714010106@stu.hrbust.edu.cn

Abstract. An autoimmune condition called rheumatoid arthritis (RA) results in long-term harm to a patient's bones and tissues. Rheumatoid arthritis is an inflammatory illness that not only damages joints but, in certain cases, can cause complications that damage other systems like the skin, blood vessels, and eyes. Modern therapies for RA include application of drugs, surgery and physical treatments aiming to eliminate the activity of RA and improve patient's living quality with the disease. Despite the rapid growth in people's knowledge about RA in the past few decades, much of RA's pathogenesis remains unknown and RA is often incurable. This article summarized some current therapies applied to treat the illness RA with evaluations of the efficacy and side-effects of each treatment involved, looking forward to providing the better theoretical foundation and information about the disease; also discussed the importance of developing new therapies involving different types of medicine as well as distinctive treatments for RA patients of different genders and backgrounds in the future.

Keywords: Rheumatoid Arthritis; treatments; theoretical foundation.

1. Introduction

The global RA prevalence was then estimated to be 0.46%, the risk of developing the disease increases with age, it usually occurs among people with ages from 40 to 50 years. RA is on average about 3-5 times often observed in women than in men [1]. For women that are diagnosed as RA patients, there is evidence that they will have families of smaller sizes than those who are healthy. 3 reasons are suggested: firstly, the application of anti-rheumatic drugs is associated with damaged fertility and increased risk of abortion for women. Secondly during the active stages of RA statistics have shown lower pregnancy rates, probably due to damage of RA on patients' tissues. Finally earlier menopause is observed in women diagnosed with RA, reducing their fertility [2]. There is evidence that the RA also has relationship with genes. The probability of a monozygotic twin being given birth by RA patients to develop RA is around ten percent, a number of about 4 times the risk for dizygotic twins under same circumstances. The incidence rate of RA observed in these twins is way higher than the incidence rate of average people as well.

The pathophysiology and origin of RA involve the interaction of genetic predisposition and stimulants from the environment. Although the specific causes of RA are not fully understood, some highly possible factors increasing the population's incidence of RA that have been identified in epidemiologic studies can be avoided, including unhealthy eating patterns and breathing in toxins from smoking. Currently clinical treatment for RA, due to the chronic and subtle nature of RA, often aim to reduce the disease activity of RA instead of aiming to cure RA. In RA, there are a number of comprehensive scales to measure activity of the disease so the effectiveness of treatments can be quantitatively measured. The Clinical Disease Assessment Index (CDAI) and the 28-joint Disease Activity Score (DAS-28) are two examples. Rheumatoid arthritis disease activity is closely monitored continuously, and when the disease reaches different stages, treatment plans and medicines are adjusted accordingly. Complete suppression of disease activity is required. Most treatments for RA include medicines as the majority, while in severe cases surgeries are required to replace eroded joints and bones. Physical treatments are also common for the recovery of function of tissues in RA patients. Currently most research done were clinical studies and trials. These studies are needed to be organized and compiled to give individual treatments for patients. Hence, the key point of current research in rheumatoid arthritis is to better understand how pathologic mechanisms drive individual RA progression so that therapies can be developed that appropriately care for patients at every step of the

course of their illness [3]. This article provides an overview of treatments for RA in order to offer a better theoretical basis.

2. Pharmacologic Treatment

Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have been used to effectively treat joint stiffness and discomfort associated with rheumatoid arthritis. Instead of slowing the disease's course, though, they have only really improved the patient's quality of life. Therefore, over the past two decades, new DMARDs (disease modifying anti-rheumatic drugs) have gained much attention because they can actually reduce disease activity and significantly slow down the joint deformities caused by the disease [4]. Trying to apply DMARDs in the treatment of RA has been a major challenge for patients with rheumatoid arthritis [5]. Therapeutic classifications include new potential small compounds, biological DMARDs, and conventional synthetic medicines. DMARDs which were once studied are currently rarely implemented clinically as part of modern therapies. Many types of biological DMARDs have appeared lately, and it is suggested that more research is emerging in this field.

2.1. Steroids

Steroids have been proven to be some of the most effective drugs in reducing structural erosive damage caused by RA. A randomized, double-blind study, including a few hundred patients being diagnosed to have RA of no more than 2 years in comparing 7.5mg daily prednisolone to the placebo added to the typical and original DMARD therapy. In this experiment Larsen-radiological method was applied and smaller unit scores refer to less bone loss. The disease became more severe in the first year at an average of 0.73 units in the prednisolone group, compared to a much higher 3.63 units in the placebo group. This shows that compared to typical DMARD treatment, treatment involving prednisolone reduced level of structural damage in RA patients. Just 22% of individuals who had taken prednisolone exhibited radiographic erosions after a 2-year follow-up, compared to a much larger proportion of 45% of patients who had received a placebo. Following the cessation of prednisolone treatment after two years, there was an observed increase in radiological damage in the third year [6].

But steroid therapies are not without issues and constraints. An important issue associated with glucocorticoid abuse and prolonged use is the heightened susceptibility of patients to infections. The risk of infection is raised by the longer treatment duration and higher dosage of glucocorticoids. The relative risk of infection was roughly two, according to a meta-analysis of around one hundred studies included two thousand RA patients with different glucocorticoid dosages and symptoms with confidence interval of 95% [7].

2.2. NSAIDs

The use of Nonsteroidal Antiinflammatory Drugs (NSAIDs) in rheumatology is widespread. The chemical classes of NSAIDs vary widely, but all have the property of blocking prostaglandin (PG) production [8]. This is achieved by reducing the combining affinity of the PGG synthase [9]. When treating RA symptomatically, NSAIDS make patients have pain relief with less adverse effects than glucocorticoids, while not being as effective anti-inflammatory medications [10]. Research has proved that appropriate dosages of NSAIDS can be combined with DMARDs and glucocorticosteroids in later stages of RA treatment to control the disease process [10].

However, the adverse effects of NSAIDS are also considerable. A common side-effect of NSAIDS is stomach problems such as nausea and diarrhea. Also, as prostaglandin production inhibitors, NSAIDS may cause disorder in patients' renovascular homeostasis. Up to 25% of NSAID-treated patients have been observed to experience salt retention, which may be more noticeable in individuals who already have a predisposition to Na⁺ [11]. Patients taking NSAIDs may experience peripheral

edema and weight gain due to decreased salt excretion. This response may be significant enough to cause clinical disorders.

2.3. DMARDs

Disease-modifying antirheumatic drugs (DMARDs) are drugs developed in order to treat inflammatory arthritides including RA. DMARDs are classified as either conventional DMARDs or biologic DMARDs, and they are usually immunosuppressive and immunomodulatory drugs. Among the often prescribed conventional DMARDs include leflunomide and methotrexate (MTX). On the other hand, since their introduction in the early 1990s, biologic DMARDs have been prescribed mostly in cases when conventional DMARD therapy has failed. Some biologic agents include TNF- α inhibitors and belimumab, in this section conventional DMARD MTX and leflunomide will be introduced while biologic DMARD TNF- α inhibitors and belimumab will be introduced.

2.3.1. Methotrexate

Methotrexate is a conventional synthetic DMARD, or sDMARD. Methotrexate is a modified form of folic acid. It has a higher binding affinity for dihydrofolate reductase (DHFR) than its parent molecule and is often considered one of the most powerful drugs for the treatment of RA. Methotrexate has shown favorable therapeutic effects both alone and in combination with other DMARDs [12]. At a conference organized by the Sociedad Española de Reumatología (SER), one of the first conclusions discussed by a panel of specialized physicians was that patients should start synthetic DMARD therapy immediately after being confirmed to have RA in order to achieve the desired low disease activity. A clinical trial evaluating levels of hand bone loss in early RA patients using digital X-ray radiogrammetry has shown that over 10% less bone loss was observed in patients applying MTX treatments [13].

Studies have demonstrated that, when compared to other disease-modifying antirheumatic medications or a placebo, patients with RA who used MTX for at least six months did not significantly increase their risk of developing cancer, proving the safety of MTX in malignancy. However, a retrospective case conducted on 28 patients in Sheba Medical centre who suffered from toxicity of low dosage of MTX has pointed out the potential myelosuppression effect of MTX: among the 28 patients included by the study, 7 eventually died from sepsis caused by toxicity of MTX but the concentration of serum MTX varied little between patients that died and survived [14]. Another 6-year open perspective study has revealed the positive correlation between MTX treatment and increased chance of opportunistic infections [15].

2.3.2. Leflunomide

Leflunomide is classified as a disease-modifying antirheumatic drug, or in other words, DMARDs. It inhibits dihydrothymine synthase, which is required for transcription and DNA replication. Over-active immune cells with high rates of mitosis and protein synthesis are hence suppressed, thereby reducing inflammation in ankles caused by hyperactive immune response, especially by the proliferating lymphoid cells. At higher volumes, the metabolite of Leflunomide, triflumamide demonstrated inhibition of production of proteins acting a critical role in initial lymphocyte signaling [16]. Leflunomide is an important medicine in RA pharmacotherapy: the clinical and functional therapeutic efficacy of leflunomide have similarities with that of MTX. Leflunomide has also been shown in practice to be effective in combination with biologics.

The adverse effects of Leflunomide are present in some patients. A 52-week study involving treatments of Leflunomide against RA, despite a 41% to 61% improvement in uncomfortable symptoms caused by RA, more than 5% of all patients reported allergic reactions, asthenia, abdominal pain, back pain and hypertension [17]. Rare cases are reported where Leflunomide affects the lungs, as well as causing acute drug-induced liver harm. Doctors and patients should be aware of such consequences by checking the functional state of liver and lungs regularly when taking Leflunomide treatments. In terms of drug toxicity, leflunomide is harmful to the developing fetus and can harm infants through breastfeeding, and should be avoided during pregnancy and breastfeeding.

2.3.3. TNF- α inhibitors

TNF- α is a common bDMARDS target in treating RA. TNF- α causes inflammation through activated monocytes, macrophages and t cells. It binds to TNF receptors 1&2. The binding between TNF and its receptors activates important pathways in apoptotic signaling. Meanwhile, TNF- α is also involved to induce neovascularization and the release of cytokines promoting inflammation. In RA, TNF- α induces systemic bone loss in patients. Inhibitors of TNF- α (TNFi) hence improves health conditions of patients and reduce damage in the bones of joints [18]. Current experimental data suggests that TNFi are also effective in mitigating the risk of arterial stiffness and myocardial infarction associated with rheumatoid arthritis in cases of rheumatoid arthritis.

Some studies show that TNFi can have serious adverse effects on patients--specifically, higher risks of infection and tumourgenesis. A study compared incidence of malignant tumour and infections between patients applying TNF- α inhibitors and those who didn't [19]. The study's result was that individuals with RA receiving TNFi medication had a dose-dependently elevated risk of malignancies and higher probability of serious infections. The results in this experiment could have been to some extent biased and inaccurate since meanwhile other studies suggested that the application of anti-TNF therapies have no correlation with increased infection or malignancies [20].

2.3.4. Belimumab

Belimumab belongs to the family of monoclonal antibodies. It inhibits soluble human BLyS by binding to it with high affinity. Patients with rheumatoid arthritis have elevated levels of BLyS in their serum and synovial fluid, which is linked to elevated RF levels. The BLyS method of action is critical for B cell survival, and autoimmune B cell clones that are inhibited undergo apoptosis. In the Phase II trial of Belimumab comparing improvement in conditions of patients of RA distributed into placebo groups and groups taking Belimumab, Week 24 ACR20 responses with placebo and belimumab 1, 4, were 15.9%, 34.7% ($p = 0.010$), 25.4% ($p = 0.168$), and 28.2% ($p = 0.080$), respectively [21]. This result showed the advanced efficacy of Belimumab in treating RA. Other promising CD-20-targeting antibodies similar to Belimumab such as obinutuzumab and ibritumomab require additional clinical trials since the strategies provided by these monoclonal antibodies seek for deep reduction in B-cell populations, which is not a better approach than inhibiting B-cell-regulated cytokines.

3. Surgery & Physical Therapy

Under circumstances where pharmaceutical treatments fail to improve life qualities, surgeries aiming to replace or repair bones and joints are going to be considered. Surgery can relief pain associated with the disease and improve joint function. Surgery for rheumatoid arthritis may involve synovectomy, tendon repair, fusion and total joint replacement. Knowing when is the time for surgery for specific patients is necessary for rheumatologists. Though most RA patients do not need surgeries, people confirmed to have RA should always listen to their doctors' advice on the timing of surgeries if necessary [22].

Physical therapy for rheumatoid arthritis is designed to give the patient appropriate exercise to keep the joints active and to avoid placing undue stress on the painful joints, and is often used in addition to other therapies to promote symptomatic relief of the disease. As a conservative therapy, it often involves therapist-developed aerobic exercise aiming to reduce fatigue caused by RA and improve sleep quality of patients. Moderate levels of exercise can as well improve the mobility of joints for RA patients, retaining part or, fortunately, the majority of their original function [23].

4. Limitations

The arthritis rheumatoid Clinical response heterogeneity to various therapies. Some patients have low disease activity or clinical remission, making them difficult to treat and making it difficult to achieve therapeutic objectives. Treatment failure may coexist with known risk factors, such as the

existence of hereditary characteristics, autoantibodies, joint erosions, comorbidities, extra-articular symptoms, and pregnancy or desire for pregnancy. It is notable that RA has a much higher incidence rate of females than males, but this statistical fact have multiple causes beside genetic variances. Females and males have different Pharmacokinetics mechanisms. For drugs applied in RA treatment, however, current studies haven't established relationship between gender and optimal treatments for patients. This can be a research topic for tomorrow's researchers. In order to reduce disease activity of RA for every patient, researchers should distinguish the best therapies for people of complex biological and social differences.

5. Conclusion

In recent years, the research content of RA treatment is relatively rich, and great progress has been made. Many types of treatment methods have been discovered and passed clinical trials and applied in clinical practice. However, different therapies have advantages and side effects, and people of different genders and different environments may have different responses to different therapies, so further research is needed. There is still a lack of large sample clinical data and evidence-based medical evaluation for close monitoring of therapeutic drugs, and its feasibility and universality need to be studied and cannot be generalized. Some new drugs such as targets are also entering the clinic, many of which are blockbuster drugs with good prospects, and are expected to break the bottleneck of RA treatment in the future. It can be predicted that the discovery of fast and efficient, continuous control, high safety of RA diagnosis and treatment methods is the goal of the future common struggle.

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