Chemical Medicines and Biopharmaceuticals in Rheumatoid Arthritis

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Abstract. Rheumatoid arthritis is a disease caused by autoimmunity that results from a series of almost lifelong processes. Over decades, researchers have studied its cause and risk factors and many types of drugs for treating RA have been developed and approved. This article provides a comparative analysis of chemically synthesized disease-modifying anti-rheumatic drugs (sDMARDs) and biologic DMARDs (bDMARDs) in the treatment of rheumatoid arthritis (RA). While both aim to alleviate inflammation and prevent joint damage, their mechanisms of action differ significantly. sDMARDs broadly suppress immune cell activity, whereas bDMARDs target specific cytokines or pathways with higher selectivity. Clinical studies indicate that bDMARDs generally offer a faster onset of action, but long-term efficacy is comparable to sDMARD-based therapies. Safety profiles also diverge, with sDMARDs posing greater risks of organ toxicity, particularly hepatotoxicity, while bDMARDs increase susceptibility to infections and potential malignancies. Economic evaluations highlight the lower cost and higher accessibility of sDMARDs, solidifying their role as first-line treatments, despite the clinical advantages of bDMARDs and faster response rate.

Keywords: Rheumatoid arthritis, disease-modifying anti-rheumatic drugs, synthetic DMARDs, biologic DMARDs.

1. Introduction

Rheumatoid Arthritis (RA) is a disease where the immune system targeted self-generated tissues and attack them causing joints and bones to swell and be damaged seriously. Although people usually get diagnosed with RA around their middle-ages, the immunology studies actually indicated that RA was a chronic disease due to a lifelong process where the immune system identifies modified self-protein as foreign protein and produces autoantibodies. This process may appear even decades with no clinical symptom and there is no effect on patients' health. However, DNA in T cells in the immune system start to become unstable and cause T cells to act abnormally. As a result, T cells become more aggressive towards tissues. Around middle age of life, the irreversible failure of tissue tolerance occurs and cause synovitis. The synovitis turns into chronic inflammation quickly, and triggers several processes that leads to RA and damage to the joints and bones [1].

The exact reason for the autoimmunity in RA is still under investigation, but there have been several risk factors proposed to be related to RA morbidity, including age, sex, environmental and genetic factors. Over decades, researchers have confirmed that women have a higher possibility to get RA than men and there were meta-analyses on smoking elucidating that the possibility of getting RA was higher for men than that for women and for those smokers who are highly addicted to tobacco than those who are less addicted to [2]. Besides, people are considered to be more likely to get RA if they have a family history of RA and Frisell et al had found that the possibility of RA was 40% heritable and seropositive RA had a higher heritability than seronegative RA [3]. The prevalence of RA is also varied with the country and region where people live in. For example, it was found that the prevalence of RA in adults was the highest in Australia and New Zealand and the disease was rare in Sub-Sahara according to a review published by Shapira et al in 2010 [4]. Furthermore, there were numbers of papers indicated that there were higher chances for people lived in cities to get RA than those who lived in rural areas and the exact reason for these regional differences is still not determined [5]. In general, RA prevalence is 0.24% to 2% of the population worldwide approximately and the

researchers have carried on decades of studies to find proper treatments for dealing with this lifelong disease[5].

Although there have been advanced developments on treatment in RA after decades of researching, it is still hard to find a strategy for curing RA completely due to its complex and multifactorial property. Modern treatments focus on alleviating the inflammation and prevent the disease from further damaging the joints and bones. Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are the most popular medicines developed to treat RA. The purpose of using DMARDs in RA treatments is not only for improving the condition of patients which has been achieved by Non-steroidal Anti-inflammatory Agents (NSAIDs), but also for affecting the course of the disease, modify it and ultimately prevent the damage in joints and bones. DMARDs are classified by the way they are manufactured. Synthetic DMARDs (sDMARDs) are small molecules obtained from chemical synthesis and developed as chemical medicines and biologic DMARDs (bDMARDs) are generally large protein molecules developed as biopharmaceuticals. These kinds of drugs have received a lot of attention from researchers and huge number of papers have been published focusing on different aspects such as efficacy and safety studies. The main interest of this article is to compare the applications of sDMARDs and bDMARDs in treatments of RA and analyze their overall benefits and drawbacks when acting as individual therapies to determine the proper way and time to use sDMARDs or bDMARDs during the treatment of RA.

2. Comparison of Chemical Medicines and Biopharmaceuticals

2.1. Working Principles and Targets

2.1.1 Synthetic disease modifying anti-rheumatic drugs (sDMARDs)

Although the ultimate goal of chemical medicines and biopharmaceuticals is the same, the mechanisms of action and targets of chemically synthesized medicines (sDMARDs) and biopharmaceuticals (bDMARDs) towards rheumatoid arthritis (RA) are completely different. sDMARDs are broadly categorised into two groups, conventional sDMARDs (csDMARDs) and targeted sDMARDs (tsDMARDs). The general principle of csDMARDs is to block the lymphocyte cells, like B and T cells and stop them from proliferation so that the joint inflammation is alleviated and cured. For example, the mechanism of the efficacy of methotrexate, one of the most commonly used csDMARDs in the first-line clinical treatments of RA, has been investigated for decades since it was proved to be effective towards treating rheumatoid arthritis. Several hypotheses have been established and it is more and more common to explain the anti-inflammation mechanism of methotrexate towards RA using adenosine signaling (Figure 1). It is proposed that methotrexate blocks a kind of enzyme that increases the intercellular AICAR levels, leading to an increase in extracellular adenosine levels. The extracellular adenosine interacts with receptors and triggers several pathways, such as inhibiting the activation of T and B cells and cell proliferation is prevented and hence the anti-inflammatory effect [6].

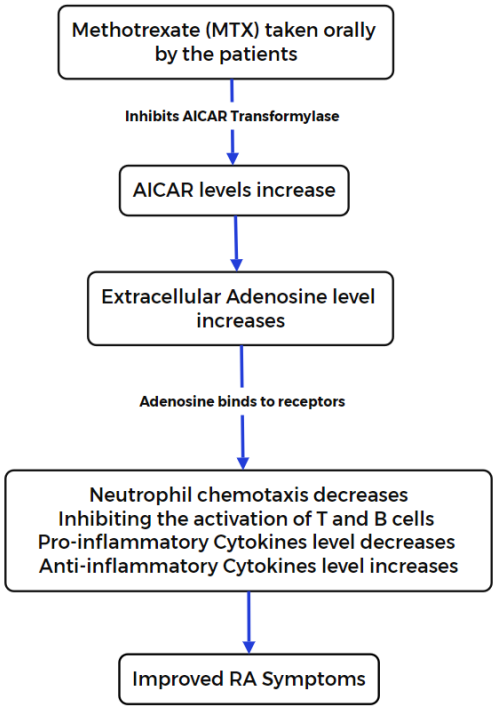


Fig. 1 A flowchart on mode of action of methotrexate in RA [6]

As the other group of sDMARDs, tsDMARDs are more target-specific than csDMARDs because they are usually synthesised to target a specific signaling pathway in the cell. Janus kinases (JAK) inhibitors are the most common group of tsDMARDs that target the JAK-STAT (Signal Transducers and Activators of Transcription) pathway. This pathway is triggered by cytokines interacting with receptors, leading to JAKs activation. As a result, the STATs are phosphorylated and dimerised and trigger transcriptional response that causes inflammation after entering the nucleus [7]. Therefore, when JAK inhibitors such as tofacitinib block the JAK-STAT pathway, the STAT and the transcriptional response will not be activated. This also reduces T and B cell activation and proliferation and abbreviates the inflammation.

2.1.2 Biologic disease modifying anti-rheumatic drugs (bDMARDs)

bDMARDs are usually considered to be more specific than sDMARDs. Instead of targeting broadly to the whole immune system or a signaling pathway, bDMARDs are developed to affect the function of one specific cytokine. For example, the earliest group of bDMARDs invented to treat rheumatoid arthritis are tumour necrosis factor-α (TNF-α) inhibitors. The target of these inhibitors is TNF-α, which is one crucial cytokine in the pathogenesis of RA. The binding between TNF-α and its receptors, usually TNFR1 and TNFR2, activates several pathways that related to ransducing signal. More proinflammatory cytokines are generated causing synovial fibroblasts and finally bones and joints are damaged [8]. Therefore, when TNF-α inhibitors are taken into patients' body, they bind with TNF-α to prevent the cytokines from binding with the receptors and triggering a series of signaling pathways that lead to joint destruction. The rest types of bDMARDs available to treat RA including T cell co-stimulation inhibitors and CD-20 depleting antibodies, have different working principles depending on the specific cytokine or immune cell they are targeting.

2.2. Speed of Response and Long-Term Efficacy

Due to their difference in targeting specificity and modes of action, sDMARDs and bDMARDs show distinct onset of action in the early treatment stage towards rheumatoid arthritis. In general, sDMARDs are considered to have a slower action than bDMARDs because they affect the immune system more broadly and gradually. According to the data from Johns Hopkins Arthritis Centre, the fastest onset of action of sDMARDs may be observed 4 to 6 weeks after the drug (methotrexate) was

taken, while the earliest onset of action of bDMARDs can be seen 2 to 4 weeks after injection (TNF-α inhibitors) [9].

In 2015, Scott et al. reported a TACIT trial where the efficacy of a combination intensive therapy with sDMARDs and TNF-α inhibitors on RA was compared. There were 432 patients enrolled in total for screening in the study and 147 of them finally completed the 12-months trial(Figure 2). The efficacy of the two groups of treatments was assessed by health assessment questionnaire (HSQ) taken during the baseline and sixth and twelfth months of the study. According to the report, the sDMARDs group demonstrated a higher mean reduction HSQ scores than those of TNF-α inhibitor group [10].

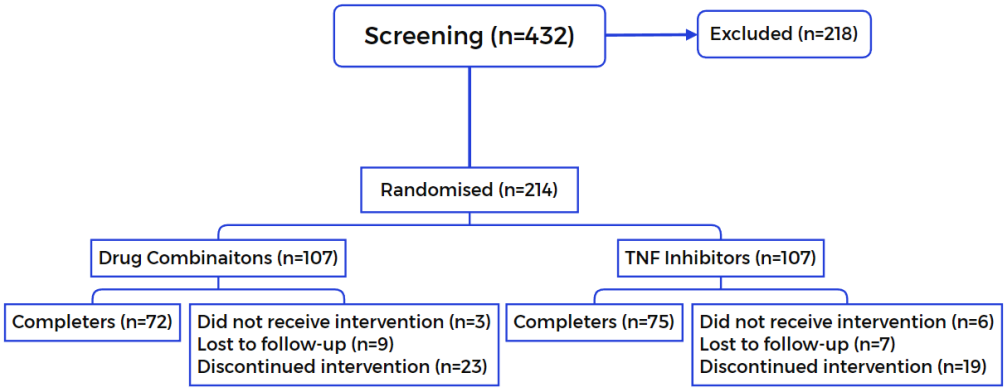


Fig. 2 The flowchart of the trial in patients conducted by Scott's group [10]

Additionally, the DAS28 scores, indicating disease activity, in patients with the TNF-α inhibitor treatment dropped more significantly than that in patients with sDMARDs treatment during the first 6 months of the trial, but the difference was almost the same at the end of the trial. These results indicated that although the TNF-α inhibitor had a quicker response at the earlier stage of treatment towards RA, the long-term efficacy of using the TNF-α inhibitor and combined treatment of sDMARDs towards RA was almost the same. Furthermore, the researchers also investigated the patients' life quality in the two treatment groups after receiving the drugs. The final results indicated an improvement in quality of life for both two groups. These scores showed a similar effect of sDMARDs combined therapy and TNF-α inhibitors treatment on patients' life quality and provided further evidence that the long-term efficacy of these two strategies on RA was almost the same [10].

2.3. Safety and Adverse Effects

Besides efficacy, safety and side effects of a drug are 2 other important concerns for patients and clinicians when choosing a proper therapy. The adverse effects of individual disease-modifying anti-rheumatic drugs might be different due to their different working mechanisms and targets. In this section, common side effects are discussed for synthetic and biologic DMARDs and specific side effects of individual drugs are also included.

2.3.1 Side effects of synthetic DMARDs

As a group of chemically synthetic drugs, organ toxicity is the most common concern about synthetic DMARDs and the toxicities are drug-specific. Although the exact mechanism remains undetermined, methotrexate is usually considered to cause damage to the liver during the therapy, especially for patients who are addicted to alcohol and have been diagnosed with liver disease [9]. Another sDMARD that is considered to have hepatotoxicity is leflunomide. Besides, both leflunomide and methotrexate have been related to myelosuppression and cause a lowering of blood counts [11]. Therefore, routine lab monitoring is needed for patients who are taking these two drugs to assess their hepatic function and blood count [9]. Hydroxychloroquine and sulfasalazine are the other two available sDMARDs. The most common side effect of hydroxychloroquine is retinal damage due to its antimalarial properties and baseline and follow-up examinations every 12 months

after receiving the drug are recommended [9]. Serious toxicity is very uncommon during sulfasalazine treatments, but there are still chances for patients to get hypersensitivity and allergic reactions [9]and leucopenia [12]. As a result, patients are suggested to take a baseline G6PD enzyme examination and blood monitoring every 1-3 months is essential for sulfasalazine therapy [9].

There are also concerns about the risk of infection after taking synthetic DMARDs. For example, it has been reported that methotrexate as well as leflunomide is related to a higher risk of infection in RA patients, while hydroxychloroquine and sulfasalazine are not associated with [12]. Additionally, methotrexate is also considered to be associated with cancer, especially lymphoma [9] However, these side effects still appear in rare cases, and methotrexate is still recognised as the first-line treatment of RA in a global prospective because of its proven effectiveness and potency towards rheumatoid arthritis.

2.3.2 Side effects of biologic DMARDs

On the other hand, the biologic DMARDs do not demonstrate organ toxicity like synthetic DMARDs, instead, they increase the risk of infection because they actually block specific signaling pathways and stop the immune system from functioning well. There have been published articles suggesting that patients with anti-TNF treatments had a 1.5- to 2.5-fold greater risk of getting severe infection than those undergoing csDMARD treatment in RA [13]. Routine infections such as upper respiratory and skin infections are very common in patients receiving TNF-α inhibitor treatment. Moreover, all the anti-TNF agents have been reported to be responsible for reactivating latent disease and causing disseminated tuberculosis (TB) and patients are recommended to be screened for latent TB before the whole therapy [9]. Other opportunistic infections, such as invasive fungal infections, have also been observed for anti-TNF treatments [9]. As with TNF-α inhibitors, other biologic DMARDs such as rituximab, tocilizumab and abatacept are also found to increase the risk of infection in a mild to severe manner [9], [12]. In terms of malignancy, TNF-α inhibitors have received a lot more attention than other bDMARDs. Although there were published articles suggesting that TNF-α inhibitors did not demonstrate an increased risk of most of the investigated cancers, like melanoma skin cancers, the prescription of TNF-α inhibitors still should be discussed with patients with pre-existing malignancy and their oncologists [9,13]. It is also worth noting that adalimumab and infliximab have been reported to be responsible for young patients to get a serious hepatocellular T-cell lymphoma, indicating the potential risk of childhood malignancies [14].

2.4. Cost-Effectiveness and Accessibility

In terms of financial cost, synthetic DMARDs are much cheaper than biologic ones due to the difference in the cost of industrial processes. This is also one of the most important reasons for synthetic DMARDs like methotrexate always being the first-line treatment strategy for rheumatoid arthritis. Moreover, sDMARDs are delivered orally, while injection or infusion is needed to deliver biologic DMARDs. The latter requires clinical equipment and trained staff, leading to a less accessibility than the former treatment.

The TACIT trial conducted by Scott et al compared the cost of TNF-α inhibitor treatment with a combined intensive csDMARDs therapy in RA. The researchers found that, with a similar efficacy and safety profile, the cost of social and health care due to the combined therapy per patient were £3615 lower than those due to the anti-TNF treatment in the first 6 months and £1930 lower in the last 6 months of the treatments [10]. Another study conducted by Joensuu et al in 2016 also demonstrated that the mean cost for bDMARDs was about 2-fold greater than that for csDMARDs (€55,371 vs. €24,879) with a small difference in medical effectiveness, indicating a lower cost-effectiveness of bDMARDs treatments in Finland [15]. In 2019, Chen et al published a report comparing the healthcare utilization and costs of bDMARDs and csDMARDs. The researchers suggested that the high cost of biologics was compensated by the lower healthcare utilization costs due to the better clinical results than csDMARDs towards RA in Taiwan [16].

2.5. Overall Analysis and Comparison

Being considered as a lifelong disease, Rheumatoid arthritis can cause severe damage to joints and bones. A recent meta-analysis demonstrated that the standardized mortality ratio (SMR) for patients who died of both any cause and specific cause with RA was 1.522-fold greater than that in the general population, independent of gender or location [17]. After decades of development, there have been a number of chemical and biological drugs invented and approved by governments to treat RA. To conclude this part of the paper, the synthetic and biologic DMARDs work on completely different mechanisms and target the immune system in various stages and manners. sDMARDs like methotrexate usually have a lower cost compared to the biologic ones and they can be conveniently taken orally, so they are more affordable and accessible for most patients. They Biologic DMARDs, on the other hand, benefit from a faster response rate and are highly selective to the target. In terms of drug safety and side effects, sDMARDs express a small possibility of infection and malignancy, but a higher level of organ toxicity indicates more careful clinical and lab monitoring is needed to check the toxicity level in the body. On the contrary, bDMARDs demonstrate no organ toxicity and a very big infection risk and patients who have been diagnosed with cancer should take the biologics with caution.

3. Conclusion

To summarize the whole article, the application of chemical medicines and biopharmaceuticals in RA treatments is compared from different aspects, including working principle, efficacy, safety and side effects and cost-effectiveness. The advantages and disadvantages of sDMARDs and bDMARDs were analyzed and concluded. Due to their promised efficacy, lower cost and higher accessibility, csDMARDs, especially methotrexate, are always used as the first-line treatment for RA. The bDMARD therapies are often suggested if the chemical medicines are not effective on the patients' conditions because they have faster response rates and are more target-specific. Hopefully, this article will act as a general guidance for patients with RA to gain some basic knowledge on both the disease and currently available treatments and help them consider carefully the options from general efficacy, safety and economic perspectives based on their own health conditions and affordability. However, the research on sDMARDs focused on conventional sDMARDs and targeted sDMARDs that were more advanced and were less included during the comparison. Moreover, most of the content of the whole article was based on synthetic and biologic DMARDs acting as monotherapies in RA, whereas there have been more and more research carried out on the combination therapies with synthetic and biologic DMARDs. In future investigations, more information on targeted sDMARDs needs to be included and there should be more attention paid to the recent development of the combination therapies on rheumatoid arthritis.

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