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Review ETPM

DMARDs, Biologic Agents and Novel Experimental Strategies in the Treatment of Rheumatoid Arthritis

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Abstract

An inflammatory and autoimmune disease, rheumatoid arthritis (RA) causes severe pain and inflammation in affected areas of the body. According to the report, there is no known cure for RA. Therefore, reducing discomfort and halting future harm must be the goals of present therapy. For the purpose of prevention and to reduce disease activity in RA patients, significant success has been achieved with the continued development of disease-modifying antirheumatic drugs (DMARDs). The inflammatory synovial joints that characterise rheumatoid arthritis (RA), a chronic autoimmune illness, cause joint degradation, incapacity, and a reduction in quality of life. Treatment for RA has advanced significantly over the years, especially with the advent of biologic medicines, disease-modifying anti-rheumatic medications (DMARDs), and creative experimental approaches. Unfortunately, some patients continue to respond poorly to DMARDs, thus it is necessary to develop new targets and treatments in treatment of RA. The foundation of RA treatment is the use of DMARDs, with methotrexate being the most effective option. Due to their ability to specifically target immune system components implicated in the pathophysiology of RA, biologic medicines have completely changed the way that the illness is managed. Clinical outcomes and disease activity have been demonstrated to be significantly improved by tumour necrosis factor (TNF) inhibitors, such as adalimumab and etanercept. Several biologics targeting B cells, T cells and interleukin-6 (IL-6) have also been added to the therapeutic armamentarium, expanding the options available to patients who do not respond to or respond to conventional medications. These medications delay the progression of illness and maintain joint function by lowering inflammation and inhibiting the immune system. But some patients may not react well to conventional DMARDs, thus other treatment alternatives must be investigated. Finding potential therapeutic targets and methods could be made easier by comprehending the pathogenetic roles played by the various molecules in RA. With a focus on the mechanisms that cause inflammation and the creation of new drugs for blocking the various modulators in RA, this review discusses both existing and emerging targets, including proteins.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune condition that causes the synovium in joints to progressively swell, resulting in discomfort, loss of function, and deformity shown in Figure 1 [1–2]. It is characterised by a protracted polyarticular synovial inflammatory

response, which ultimately results in the articular cartilage and bone of the afflicted joints being destroyed [3]. Rheumatoid arthritis can ultimately result in increasing disability and early mortality [4–8]. Approximately 1% of the global population is affected by rheumatoid arthritis (RA), a chronic inflammatory disorder that predominantly impacts middle-aged women [9]. Between the ages of 30 and 50 is when rheumatoid arthritis often manifests as symmetrical polyarthritis of both major and small joints [10].

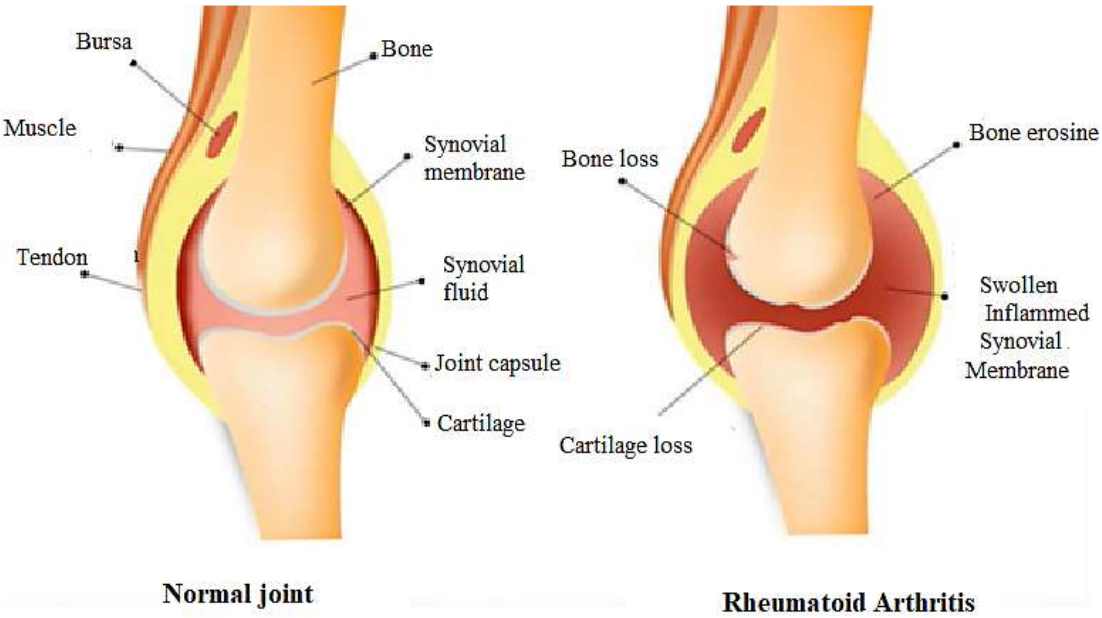

Figure 1. Represents rheumatoid arthritis.

Signs and symptoms

- Tender, warm, swollen joints
- Joint stiffness that is usually worse in the mornings and after inactivity
- Fatigue, fever and loss of appetite

Sites affected include the bones, nervous system, bone marrow, skin, eyes, lungs, heart and kidneys [11].

Risk Factors

- *Sex:* Women are more likely than men to be affected with rheumatoid arthritis.
- *Age:* Rheumatoid arthritis can affect people of any age, but it typically first manifests in middle age.
- *Family history:* If you have a family history of rheumatoid arthritis, you may be more vulnerable.
- *Smoking:* Smoking increases your risk of getting rheumatoid arthritis, especially if you have a genetic propensity for the condition. Additionally, smoking seems to be linked to a worsening of disease symptoms.
- *Weight gain:* Overweight people appear to have a slightly increased risk of developing rheumatoid arthritis.

Causes

Hormonal, reproductive, and environmental factors, as well as host factors, genetic and epigenetic factors, smoking and other airborne exposures, and diet. There are conceptual explanations for

rheumatoid arthritis fatigue (Figure 2).

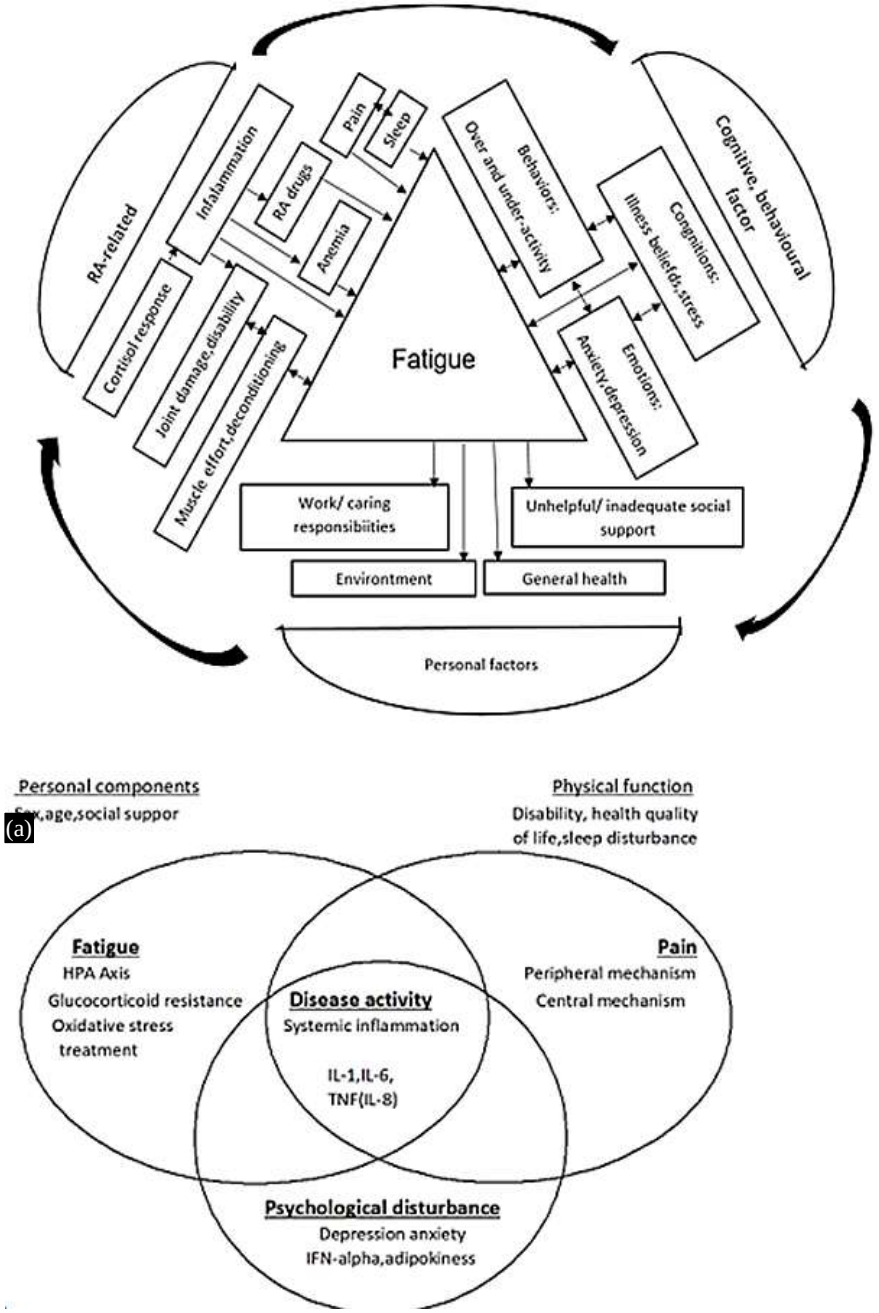

Figure 2. (a-b) Causes of rheumatoid arthritis.

The most inclusive of these models, put forth by Hewlett (Figure 2, panel a), exemplifies the notion that fatigue caused by rheumatoid arthritis most likely has numerous and varied sources [12]. Although less complete, the Louati and Berenbaum model [13] demonstrates how exhaustion may coexist with pain and sadness, two major symptoms of rheumatoid arthritis (Figure 2, panel b). Matcham provided a conceptual framework that only included psychological and cognitive aspects (Figure 2, panel b) [14]. The following sections cover characteristics that are not specifically associated with rheumatoid arthritis but have been shown to or may be associated with fatigue in rheumatoid arthritis. These factors fall into four major categories: physical, behavioral, psychological, and other psychological factors. [15]

Diagnosis

- The erythrocyte sedimentation rate (ESR), sometimes called the "sed rate," is an indicator of inflammation in your joints.
- The C-reactive protein (CRP).
- Approximately 80% of RA patients have rheumatoid factor positivity tests results (RF).
- Approximately 60% to 70% of rheumatoid arthritis patients have antibodies against cyclic citrullinated peptides (CCP) (proteins).
- X-rays, ultrasounds, and other imaging procedures may be used to diagnose rheumatoid arthritis.
- MRI scans, or magnetic resonance imaging [16].

Pathophysiology

The precise aetiology of RA is still not well understood due to the complexity of the physical and chemical characteristics, genetic variables, and environmental factors involved. But RA's harmful inflammatory components shown in Figure 3 [17]. The complicated interaction of genetic, external environmental, and individual risk factors (such as smoking, periodontitis, and gut flora) is part of the complex aetiology of RA. Due to their complex roles, rheumatoid factor (RFs) and anti-citrullinated protein antibodies (ACPAs) were overexpressed. This caused B cells, T cells, and macrophages to become activated, which in turn led to the production of inflammatory factors, which mainly include tumour necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1 (IL-1) [18–21]. These inflammatory components eventually cause joint erosion by destroying cartilage and bone (Figure 3).

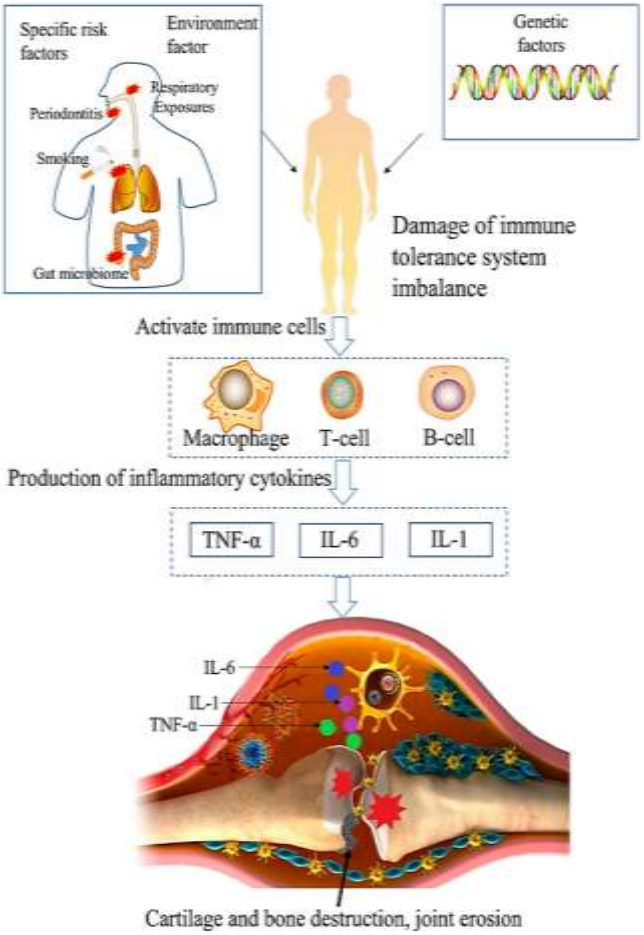

Figure 3. The mechanism diagram of inflammatory factor.

Innate and adaptive immune responses must cooperate in a healthy immune response to defend against invading organisms. The innate immune system is made up of cellular and molecular elements

including neutrophils, macrophages, and complement that engage with foreign antigens instantly and in an unspecific way while also presenting the antigens to the adaptive immune response. To remove or neutralise the effects of foreign antigens that are not fully controlled by the first reaction, the adaptive immune system responds with a more delayed but focused c response. T and B cells make up the majority of the adaptive response, which modulates a response in accordance with the triggering antigen, environmental circumstances, and host factors. Typically, this causes an increase in the production of antibodies and "cytokines," which are molecular inflammatory mediators. Cytokines provide communication between numerous parts of the immunoinflammatory response Numerous cytokines, including interleukin (IL)-1, IL-6, and IL-17 that cause inflammation are countered by cytokines like IL-4 and IL-102 (Figure 4) [22, 23].

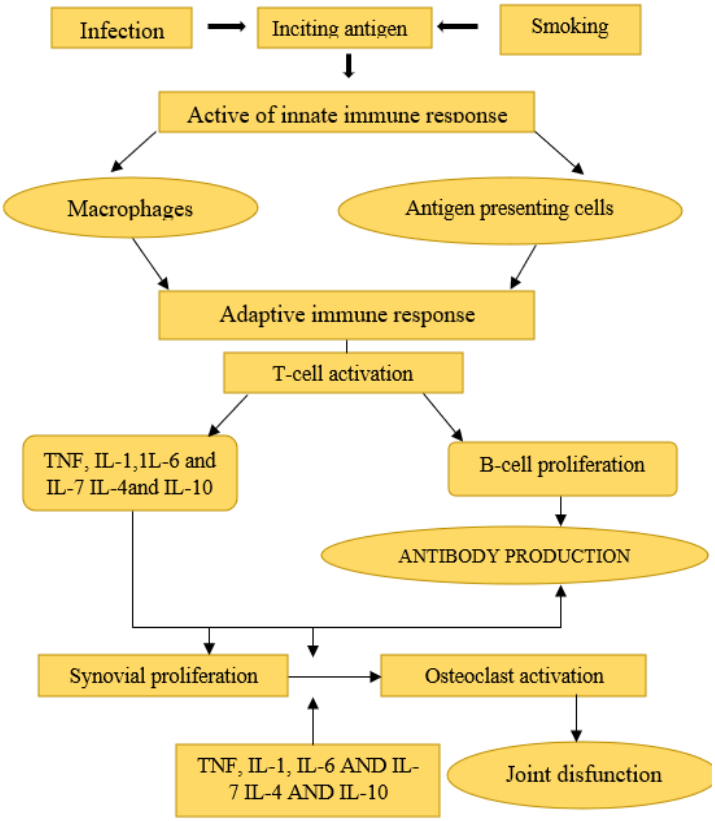

Figure 4. Schematic representation of mechanisms involved in the pathogenesis of rheumatoid arthritis

Treatment

Treatment with disease-modifying antirheumatic medications should be assessed for all rheumatoid arthritis patients. Early use lowers the disease's course and enhances the long-term outlook overall. Rheumatologists agree that rheumatoid arthritis should be treated aggressively and early, but a number of topics (such as the choice of initial medication, the timing and patient requirements for beginning combination therapy, or the use of biologics) are still being researched. A method that is supported by the current evidence is as follows.

Patients with mild disease, usually affecting five joints and associated with mild subjective symptoms, as well as normal radiographic findings, may be managed with treatments such as hydroxychloroquine, sulfasalazine, minocycline, or potentially methotrexate. In cases of moderate to severe disease (typically involving 5 or more joints, or large joints with significant subjective symptoms) or radiographic signs of bone loss or erosion, methotrexate remains the preferred first-line

treatment. If tolerated, the goal dose (15 mg/week) should be attained in 6–8 weeks shown in Table 1. Leflunomide, azathioprine, or combination therapy (methotrexate with another drug) may be explored if the response is insufficient. Compared to single-drug regimens, combinations of disease-modifying antirheumatic medications may be more successful [24]. This covers elements such disease progression, affected joints, age, general health, occupation, compliance, and disease awareness [25].

Table 1. Rheumatoid arthritis treatment: disease-modifying antirheumatic drugs and biologic agents [26].

Drug	Dosage	Onset of effect	Adverse events	Monitoring
Abatacept	500–1000 mg (weight based) every 4 weeks starting at 0, 2, and 4 weeks.	2-12 weeks	ISR, infections, sensitivity, and COPD flare-up	Perform baseline and infusion-specific CBC, chemistry, and LFTs; check for TB and other infections.
Adalimumab	40 mg twice a week	2-12 weeks	infections, TB, demyelinating diseases, and ISR (rare)	TB, fungal, and other infections; baseline and then every two to three months for CBC and LFTs
Anakinra	100 mg per day	4-12 weeks	Hypersensitivity, infections, leucopenia, and ISR	CBC at the start and every three months
Azathioprine	50-150 mg per every day	2-3 months	infections, cytopenia, hepatitis, and GI intolerance	CBC, LFTs initially every 2-4 weeks, then every 2-3 months.
Cyclosporine	2.5–5 mg per every day	2-3 months	infections, cytopenia, hepatitis, and GI intolerance	Initial CBC, LFTs every 2-4 weeks, then every 2-3 months
Etanercept	50 mg once per week or 25 mg twice per week	2-12 weeks	infections, TB, demyelinating diseases, and ISR (rare)	TB, fungal, and other infections; baseline and then every two to three months for CBC and LFTs
Leflunomide	20 mg per day	4-12 weeks	hepatitis, a skin rash, cytopenia, and GI intolerance; highly teratogenic	Serology for hepatitis B and C in high-risk patients; CBC, Cr, and LFTs every two to six months at first; dose reduction or cessation if LFTs rise
Methotrexate	15–25 mg orally, subcutaneously, or intramuscularly each week	1-2 months	oral ulcers, alopecia, hepatitis, pneumonitis, cytopenia, rash, and GI intolerance; teratogenic	CBC, Cr, and LFTs six times a month for the first two to three months; change dosage or stop if LFTs rise
Minocycline **Rituximab**	twice daily 100 mg 1000 mg at days 0 and 15.	1-3 months 2-12 weeks	CBC, Cr, and LFTs six times a month for the first two to three months; change dosage or stop if LFTs rise	none Check for TB and other infections; perform CBC, chemistry, and LFTs at baseline and every 2 weeks for the next 2-3 months.
Sulfasalazine	2-3 gm per day	1-3 months	cytopenia, rash, oral ulcers, and GI intolerance	every 2 to 3 months, CBC

First-Line Management: NSAIDS and Corticosteroids

Reducing discomfort and inflammation is often the primary goal of first aid. Nonsteroidal anti-inflammatory drugs (NSAIDs) include medications such as ibuprofen (Advil, Motrin), naproxen (Naprosyn), acetylsalicylic acid (Aspirin), etodolac, and the fast-acting drug, Lodine. When used in

high dosages, aspirin is a useful anti-inflammatory therapy RA because it inhibits prostaglandins. This was one of the first NSAIDs for treating joint pain. Aspirin overuse can result in gastrointestinal discomfort, hearing loss, and tinnitus. Aspirin is not the only NSAID there are others that are just as modern and effective [27].

Corticosteroids are a more effective treatment for inflammation even though they have a greater risk of adverse reactions than NSAIDs. Therefore, they should only be taken for only a brief amount of duration and at humble doses during RA flare-ups or exacerbations. Corticosteroid injections into the joint can treat inflammation's local symptoms [28].

Opioid Analgesics

Opioid Painkillers The issue of prescribing opiate analgesics to RA patients in pain [29]. According to their findings, mild opioids like codeine, dextro propoxyphene, and tramadol may be useful in the short-term management of RA pain, but the drawbacks outweigh the advantages. They advise considering other analgesics before opioids [30].

Second-Line Management: Disease-Modifying Antirheumatic Drugs

By reducing or preventing the development of joint damage and deformity, second-line therapy seeks to achieve remission. Because they take weeks or months to take action, medications are thought to be slow-acting. RA-related lymphoma risk can be decreased with the use of disease-modifying antirheumatic medications (DMARDs) [31]. Without FH4, the metabolism of pyrimidines and purines suffers, and the synthesis of polyamines and amino acids is inhibited. Regular blood tests are required because of the side effects of the immunosuppressive drug MTX, which include cirrhosis, liver problems, and bone marrow loss. Taking folic acid supplements can help decrease the risk of negative outcomes. It is a less harmful DMARD than others, effective, and offers dosage flexibility, enabling dose adjustments as needed [32].

Surgery

Joint surgery for RA patients reached its peak in the 1990s. A 2010 study, however, discovered that joint surgery was less common in RA patients between the ages of 40 and 59. However, rates were higher for patients over 60 [33]. A patient who requires surgery should be evaluated based on their specific needs given the range of surgeries that are available. Inflammatory tendon sheaths are removed, or a recent tendon rupture is repaired during a tenosynovectomy, which is most frequently performed on the hand [34].

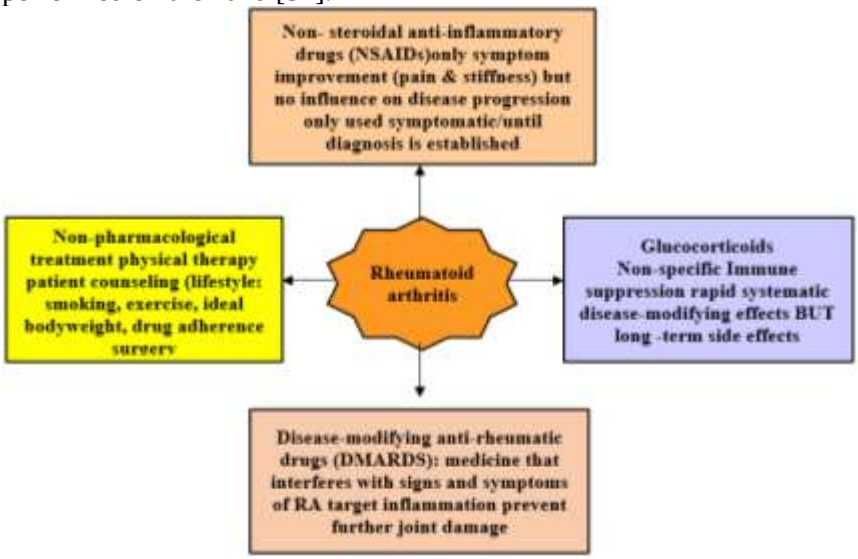

Figure 5. An overview of the treatment strategies available for RA patients

The disease's progression and the effectiveness of the employed treatment strategy should be

regularly assessed throughout the course of treatment. Up until the early 1990s, the main elements of the therapeutic pyramid used to treat RA were the administration of non-steroidal anti-inflammatory drugs (NSAID), bed rest, and disease-modifying anti-rheumatic drug (DMARD) therapy [35]. However, the effectiveness of this treatment was limited, and within a few years, rheumatoid arthritis often led to joint degeneration, disability, incapacity, and higher mortality rates [36].

The potential RA treatments consist of four fundamental strategies shown in Figure 5Non-medical treatments involve physical therapy, lifestyle counseling for the patient, and surgical options to remove or replace damaged joints and bones. Non-steroidal anti-inflammatory drugs (NSAIDs) help patients with their pain and stiffness but have little impact on how quickly the illness advances, so they are typically only used for symptomatic treatment and/or up until the RA diagnosis is made. The administration of glucocorticoids, on the other hand, results in non-specific immune system suppression that has immediate effects on disease modification but is limited in its long-term use by significant side effects. Finally, physicians and disease modifiers will administer antirheumatic drugs (DMARDs) to treat inflammation and prevent further joint damage and disease progression [37].

Aspirin, diclofenac, and ibuprofen are NSAIDs that effectively reduce pain and swelling and enhance joint function, but they do not treat disease because they do not stop further joint damage [38]. Mechanistically, the inhibition of prostanoid biosynthesis accounts for most NSAIDs' anti-inflammatory effects.

Prostanoids, which act as second messengers, regulate various cellular functions by binding to and activating G-protein coupled receptors on the cell surface. The following are examples of prostanoids: prostacyclin, thromboxane A2, PGD2, PGF2, and prostaglandin (PG) E2. Application of NSAIDs while effectively reducing RA symptoms is frequently accompanied by cardiovascular, gastrointestinal, renal, and hepatic side effects (reviewed in [39]).

Prednisolone and other glucocorticoids are extremely potent anti-inflammatory medications that slow the progression of radiologic disease in its early stages by generally suppressing gene expression [40].

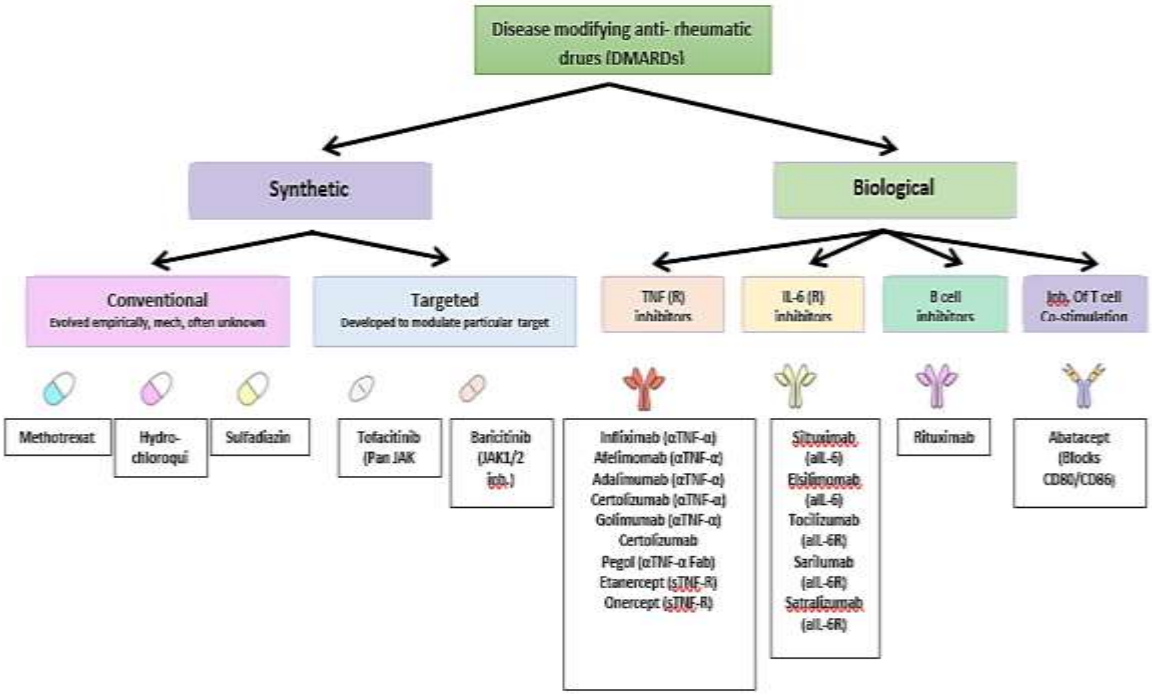

Figure 6. A summary of the DMARDs that are currently on the market.

Despite these positive effects, glucocorticoids have been shown to have limited ability to modify disease, and their long-term use is complicated by severe multisystemic metabolic side-effects like ulcer development, osteoporosis, and gastrointestinal bleeding [41].

Drugs known as DMARDs work to reduce rheumatoid inflammation and stop further joint damage. DMARDs are medications that, in contrast to medications that do not halt the progression of the disease (such as NSAIDs or painkillers), interfere with the signs and symptoms of RA, enhance physical function, and slow the development of structural joint damage [42].

The many DMARDs that are available, as seen in Figure 6, will be covered in further detail in the sections that follow.
Synthetic (and its targeted and typical synthetic subgroups) and biological DMARDs are the two categories into which the different DMARDs are separated. Examples of antibody-based biologic DMARDs include anti-TNF-TNF-R antibodies, anti-IL-6 and anti-IL-6R antibodies, anti-CD20 antibodies that deplete B cells, T-cell co-stimulation inhibitors.

Biologic DMARDs

The biological DMARDs that are currently approved have four main mechanisms of action: (1) neutralising either TNF- or the TNF receptor; (2) neutralising IL-6 directly; (3) inhibiting IL-6R and associated inflammatory signalling; and (4) depleting B cells.

TNF-α Inhibitors

These chemicals successfully reduce joint inflammation as well as damage to both cartilage and bones by neutralizing TNF-and the inflammatory processes brought on by this cytokine. TNF-inhibitors ae frequently used as second-line treatment when patients do not respond to synthetic DMDRD monotherapy, as well as combination with methotrexate or other DMARDs [43].

DISCUSSION & CONCLUSION

Effective management of a patient with rheumatoid arthritis can be achieved through early and active diagnosis, symptom control, close monitoring of the disease state and medication toxicity, and early and vigorous treatment, including biologics or disease-modifying antirheumatic medications. A specialist referral made early on can also contribute to better treatment outcomes. We now have a better understanding of the disease mechanisms thanks to developments in the field of molecular medicine, which can help in the development of more efficient treatments. Various drug combinations are currently popular methods for treating RA patients' pain and joint inflammation. Researchers are aware that current efforts are far from sufficient to recommend particular DMARDs for individual patients due to the high heterogeneity of RA. In order to choose the treatment that might be most effective for a patient, precision medicine, an emerging medical model, takes into account the genetics, environment, and lifestyle of the patient. Future research may classify RA patients into subgroups and develop precision medicine tactics to realise individualised treatment. In most patients, it is affordable and efficient to start DMARD therapy early in the disease course, with frequent follow-up, with the goal of achieving rapid and measurable disease control. The wise application of biological therapies has given RA patients hope.

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