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RHEUMATOID ARTHRITIS: CURRENT PHARMACOLOGICAL TREATMENT

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a systemic, chronic autoimmune disease that primarily affects the joints, leading to pain, swelling, stiffness, and fatigue. If left untreated, the disease may result in progressive joint destruction and deformity, long-term disability, and increased mortality.
Aim: The aim of this article is to provide a comprehensive and up-to-date overview of the current understanding of pharmacological treatment approaches for rheumatoid arthritis.
Methods: A narrative review was conducted using the PubMed, Scopus, and Google Scholar databases. The review included original research articles, systematic reviews, and clinical guidelines, published in English between 2018 and 2025, with particular emphasis on evidence from 2021 to 2025. Results: Analysis of current original research articles, systematic reviews, and clinical guidelines shows that pharmacological treatment of rheumatoid arthritis effectively controls disease activity, reduces pain and inflammation, and slows the progression of joint damage.
Conclusions: Pharmacological therapy is key to the treatment of rheumatoid arthritis. For optimal results, therapy should be individualized, taking into account disease activity, other health problems, and drug safety. New biological and targeted synthetic drugs have substantially improved the management of rheumatoid arthritis. However, further research is needed to assess the long-term safety of these therapies and to develop safer and more effective treatment options.

KEYWORDS

Rheumatoid Arthritis, Treatment, Pathophysiology, Dmards

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation, swelling, pain, redness, heat, and impaired joint function. It primarily affects the small joints of the hands and feet but may also involve larger joints. In advanced stages, symptoms may include morning joint stiffness, deformities, bone erosion, skeletal muscle atrophy, and damage to ligaments and tendons.

The disease may also affect extra-articular organs, such as the heart, lungs, kidneys, eyes, digestive system, skin, and nervous system. Extra-articular manifestations include vasculitis, pericarditis, pleuritis, pulmonary fibrosis, pleural effusion, rheumatoid nodules, glomerulonephritis, interstitial renal and lung disease, and ocular manifestations such as keratoconjunctivitis sicca, episcleritis, scleritis, and keratitis [1].

Rheumatoid arthritis is a global disease, with a prevalence ranging from 0.5% to 1% worldwide. It is almost three times more common in women than in men, although this difference is not as big in older age groups [2]. In the year 2021, an estimated 260,000 people in Poland had rheumatoid arthritis [3]. RA is a significant economic problem for patients and healthcare systems [4].

The goals of RA therapy are to relieve pain, control inflammation, and achieve remission or low disease activity [5]. The use of disease-modifying antirheumatic drugs (DMARDs), particularly of biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), has enabled remission in many patients.

2. Pathophysiology of Rheumatoid Arthritis

While progress has been made in understanding the causes of rheumatoid arthritis, the exact trigger of the disease is still unknown. No single factor is solely responsible. RA is thought to result from a combination of genetic, environmental, and metabolic factors [6].

In the pathogenesis of RA, factors such as tobacco smoking, air pollution, viral and bacterial infections, and gastrointestinal microbiota can induce inflammatory processes and lead to protein modification through

citrullination [7,8]. Genes such as *HLA-DR1* and *HLA-DR4* contribute to the loss of immune tolerance to citrullinated proteins. These proteins are taken up by antigen-presenting cells (APCs), which migrate to the lymph nodes, where they activate CD4+ helper T cells. Activated T cells then stimulate B cells to proliferate and differentiate into plasma cells, which produce autoantibodies. In rheumatoid arthritis, the main autoantibodies are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) [9].

CD4+ T cells promote inflammation, cartilage degradation, and bone erosion. Synovial macrophages in the joints release cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), and interleukin-12 (IL-12). These cytokines contribute to joint destruction and may also damage other organs [10].

3. Drugs in the Therapy of Rheumatoid Arthritis

3.1 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen sodium, meloxicam, ibuprofen, and coxibs, are used to effectively reduce inflammation and pain.

NSAIDs inhibit cyclooxygenase (COX), which exists in two isoforms: COX-1 and COX-2, each with distinct biological functions. Their analgesic effect results from the inhibition of prostaglandin production in both peripheral tissues and the central nervous system [11]. However, NSAIDs do not prevent the progression of radiographic joint damage.

Meta-analyses indicate that the long-term use of NSAIDs is associated with adverse effects such as gastrointestinal bleeding and ulcers, heart failure, renal impairment, and skin rashes. NSAIDs can also increase blood pressure and may interfere with the action of antihypertensive drugs. Studies suggest that naproxen may be one of the safer NSAIDs, while celecoxib is associated with a relatively low rate of adverse effects [12].

3.2 Glucocorticoids

Glucocorticoids (GCs), such as dexamethasone, prednisone, prednisolone, and hydrocortisone, are often prescribed in the treatment of rheumatoid arthritis due to their ability to reduce inflammation and slow radiographic joint damage [13]. The European League Against Rheumatism (EULAR) recommends using glucocorticoids as bridging therapy until methotrexate (MTX) achieves its therapeutic effect, and as adjunctive therapy when the disease persists despite the use of DMARDs [14]. However, the use of GCs as bridging therapy has limitations. A study by Hua et al. demonstrated that combining methotrexate with low-dose glucocorticoids was more effective in controlling disease activity compared with placebo, but this was only true for the first 12 months [15]. In contrast, the American College of Rheumatology (ACR) guidelines advise against the routine use of glucocorticoids because of the risk of side effects [16].

Long-term glucocorticoid therapy can lead to muscle weakness, endocrine disorders, osteoporosis, diabetes, weight gain, water retention, bone fragility, and immunosuppression [17]. The use of very low doses of glucocorticoids (<5 mg/day) is associated with an increased risk of cardiovascular diseases, such as hypertension and myocardial infarction [18]. Studies have shown that short-term use (<3 months) and low-dose treatment (>5 mg/day and ≤7.5 mg/day prednisone equivalent) appear to be reasonably safe for patients [19].

Despite these side effects, many patients continue GC therapy for longer durations (>6 months) because these medications are effective in controlling disease activity and improving quality of life [15].

3.3 Conventional synthetic DMARDs (csDMARDs)

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are usually the first medications used in the treatment of rheumatoid arthritis. This category includes methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ), and hydroxychloroquine (HCQ). These drugs consistently reduce disease activity by preventing progressive tissue and joint damage.

Methotrexate is the most frequently used csDMARD. The medication acts as a structural analogue of folate, interfering with purine and pyrimidine nucleotide synthesis. The mechanisms of its anti-inflammatory effects include the activation of AICAR transformylase leading to increased adenosine production [20].

Most international guidelines recommend methotrexate as a first-line treatment for newly diagnosed RA patients. Other csDMARDs are used if methotrexate is contraindicated or not well tolerated. Methotrexate is preferred because of its efficacy, relatively good safety profile, and low cost [14,16]. However, only about 30% of patients with RA achieve remission or low disease activity with MTX monotherapy. The addition of short-term glucocorticoids may increase this proportion to approximately 60% [21]. Methotrexate is given once a week, either orally or subcutaneously. Oral MTX is preferred due to its simplicity and low cost [22].

Subcutaneous administration provides better bioavailability, particularly at higher doses, and is associated with a lower rate of gastrointestinal intolerance. However, side effects of methotrexate include diarrhea, nausea, cirrhosis, hepatotoxicity, thrombocytopenia, leukopenia, pneumonitis, and pulmonary fibrosis [23]. To reduce the chance of side effects, folic acid supplementation is routinely prescribed at a dose of 5 mg per week. Importantly, folic acid does not reduce the anti-inflammatory efficacy of methotrexate [20].

Leflunomide is a prodrug that inhibits dihydroorotate dehydrogenase (DHODH), thereby affecting different components of the immune system involved in the pathogenesis of rheumatoid arthritis. Studies have found that leflunomide induces remission in 25% of patients [24].

Sulfasalazine is a prodrug that consists of 5-aminosalicylic acid and sulfapyridine. It is recommended for patients in whom treatment with salicylates or non-steroidal anti-inflammatory drugs has been ineffective. The mechanism of its action is not completely understood. It is hypothesized that sulfasalazine and its metabolite, sulfapyridine, are absorbed into the synovial fluid, where they exert anti-inflammatory effects [25]. Like methotrexate, sulfasalazine use can lead to folate deficiency, so supplementation is often recommended [14]. The side effects of the drug include neurological and gastrointestinal symptoms, which typically occur within the first few months of treatment and are usually mild [25].

Hydroxychloroquine is an antimalarial drug. Its anti-inflammatory mechanisms include stabilization of lysosomes, regulation of cytokine production, and antigen presentation. Early studies suggested that HCQ might inhibit cartilage damage, slow disease progression, and protect against joint damage in RA patients. Recent studies have been unable to prove these positive effects [26]. Hydroxychloroquine has positive metabolic effects and reduces cardiovascular risk [27].

3.4 Biological DMARDs (bDMARDs)

Biological disease-modifying antirheumatic drugs (bDMARDs) are a class of medications that inhibit molecular pathways involved in the inflammatory processes of rheumatoid arthritis. They primarily target cytokines such as TNF-α, IL-1, and IL-6, which play central roles in the pathogenesis of RA [10]. bDMARDs are safe and effective at preventing joint damage and physical disability.

Five major classes of bDMARDs include:

- Tumor necrosis factor (TNF)-alpha inhibitors: infliximab, adalimumab, etanercept, golimumab, certolizumab
- Anti-CD20 antibodies: rituximab
- T-cell targeted therapies: abatacept
- Interleukin-6 receptor antibodies: tocilizumab, sarilumab
- Interleukin-1 inhibitor: anakinra [14]

TNF-α inhibitors are the first bDMARDs approved for RA treatment. They inhibit the cytokine TNF-α, which is produced by activated macrophages, monocytes, and T lymphocytes. This cytokine induces other pro-inflammatory cytokines, activating immune cells, endothelial cells, and suppressing regulatory T cells. Several drugs that inhibit the TNF-α cytokine are infliximab, adalimumab, etanercept, golimumab, and certolizumab.

Infliximab (IFX) and adalimumab (Ada) are monoclonal antibodies. Certolizumab pegol is a Fab fragment of a human anti-TNF antibody. Etanercept is a recombinant fusion protein consisting of two extracellular domains of the human TNF receptor linked to the Fc portion of IgG1, while golimumab is a fully human IgG1κ monoclonal antibody [28]. These drugs reduce disease activity, slow radiographic progression, and preserve joint function. According to research, TNF-α inhibitors are an effective treatment for patients who did not do well with csDMARD medications. In cases of ineffective TNF inhibitors, guidelines do not recommend a specific treatment strategy. Patients without a response to a TNF-α inhibitor might respond to another one. However, non-TNF biologic drugs were more effective than a second anti-TNF medication [29].

IL-6 is a cytokine important in initiating and maintaining inflammatory states. High IL-6 levels stimulate the production of acute-phase proteins, such as C-reactive protein, enhancing immune system activation and maintaining chronic inflammation, contributing to joint destruction and disease progression. Also, IL-6 is a central mediator of osteoclast activity, leading to increased bone resorption [30].

Tocilizumab, a humanized monoclonal antibody, blocks the receptor for IL-6 (IL-6R). The JUST-ACT trial has proven the clinical advantages of combining tocilizumab with DMARDs in patients who had an inadequate response to methotrexate [31]. Sarilumab is another human monoclonal antibody that targets IL-6R. Adding sarilumab to methotrexate was found to limit structural damage in patients who had not responded adequately to methotrexate and TNF inhibitors. This medication improves physical function, quality of life, work productivity, and reduces fatigue [32].

Anakinra is a recombinant IL-1 receptor antagonist. It is less frequently prescribed because it has lower clinical efficacy compared to other bDMARDs and requires daily subcutaneous injections [33].

Other biological DMARDs approved for the treatment of rheumatoid arthritis include rituximab and abatacept. Rituximab is a chimeric monoclonal antibody that specifically targets CD20-positive B cells and can destroy specific groups of B lymphocytes, which contribute to the inflammatory cascade [34]. Abatacept is a fusion protein comprised of CTLA-4 and the Fc segment of IgG1. It inhibits T cell activation by blocking its interaction with CD28. Abatacept is approved to treat RA patients who have had an inadequate response to at least one csDMARD or TNF inhibitor. Phase III trials have demonstrated its long-term (about 5-year) effectiveness [35].

Biosimilar drugs highly similar to the original biologic were developed. These drugs have comparable efficacy and safety and may reduce costs compared to the original drug [36].

Although biologics have revolutionized RA treatment, they are expensive, administered mainly via subcutaneous injections, and can bring risk of side effects. Up to 40% of RA patients do not respond to their first biologic or lose response over time. Some bDMARDs can cause immune response, producing anti-drug antibodies (ADAs) against the foreign protein component as well. ADAs can lead to low serum drug levels in the blood, loss of clinical response, and cause adverse effects such as infusion reactions [37]. Adverse effects of bDMARDs include neutropenia, redness at the injection site, upper respiratory tract infections, nasopharyngitis, pneumonia, atrial fibrillation, and herpes zoster. Anti-TNF medications can cause a sarcoidosis-like disease. Studies have demonstrated that the use of TNF-α inhibitors increased the risk of tuberculosis by 18-fold [38].

3.5 Targeted synthetic DMARDs (tsDMARDs)

Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) include medications called Janus kinase (JAK) inhibitors. JAK inhibitors are small orally administered molecules that inhibit intracellular tyrosine kinases (JAK). Janus kinases are proteins that play key roles in intracellular signal transduction. The JAK family contains four members (JAK1, JAK2, JAK3, and tyrosine kinase 2[TYK2]) and interacts with seven signal transducers and activators of transcription (STATs). These pathways promote the transfer of phosphate groups from adenosine triphosphate (ATP) to cytokine receptors. When cytokines bind to their receptors, they activate JAKs, which phosphorylate the intracellular domains of these receptors and recruit STAT proteins. Phosphorylated STATs translocate to the nucleus and initiate gene transcription [39].

Tofacitinib, filgotinib, baricitinib, and upadacitinib are JAK inhibitors used in RA. Each JAK inhibitor has a unique structure, causing differences in their effects on the body. Differences are seen in hematological parameters, reproductive toxicity, metabolism, and elimination [40].

JAK inhibitors have high efficacy and safety profiles, convenient oral administration, and lower production costs compared with bDMARDs [41]. Clinical trials have shown that JAK inhibitors, used either as monotherapy or in combination with methotrexate, demonstrated multi-target, rapid, and robust effects that were comparable to or even superior to those of biologic DMARDs (bDMARDs). Researchers generally agree that the short- and long-term safety profiles of JAK inhibitors are similar to those of bDMARDs. In contrast to bDMARDs, JAK inhibitors are not immunogenic and therefore generally maintain their efficacy over the course of the disease without the development of anti-drug antibodies [42].

Janus kinase inhibitors increase the risk of infections due to immune system suppression. The phase III SELECT clinical program analyzed the safety of upadacitinib and reported adverse effects such as upper respiratory tract infections, nasopharyngitis, urinary tract infections, and bronchitis, with the most serious events including pneumonia, bronchitis, and sepsis [43]. Also, research on the long-term safety of tofacitinib, with follow-up lasting up to 9.5 years, discovered no change in the rates of infections, opportunistic infections, and serious infections [44].

The effects of JAK inhibitors on the risk of malignancies, acute myocardial infarction, stroke, cardiovascular events, major adverse cardiovascular events, arterial thromboembolism, and venous thromboembolism remain unclear. Studies have found that using a JAK inhibitor with MTX did not raise the risk of cancers [45]. However, results from studies on tofacitinib have suggested a slightly higher incidence of malignancies and an increased risk of serious cardiovascular events compared with TNF inhibitors [46]. In the ORAL-Surveillance randomized trial, more adverse heart events, higher malignancy rates, and a higher infection rate were observed with the use of tofacitinib compared to TNF inhibitors [47].

4. Current International Recommendations for Treatment

Two organizations, EULAR (European League Against Rheumatism) and ACR (American College of Rheumatology), published guidelines for the treatment of RA. Both guidelines recommend a "treat-to-target" strategy, an approach in which treatment is individualized to specific goals, such as reducing joint inflammation and pain, slowing joint damage, reducing disability, and achieving sustained remission or low disease activity for at least six months [48]. The EULAR guidelines emphasize that treatment should aim to deliver the best possible care, through consensus between the patient and the rheumatologist. Treatment decisions should take into account disease activity, safety concerns, comorbidities, and the progression of structural damage [14].

Guidelines recommend methotrexate as first-line therapy. However, for patients with low disease activity, the ACR guidelines recommend starting with hydroxychloroquine or sulfasalazine. EULAR supports starting treatment with methotrexate with glucocorticoids as a bridge as conventional synthetic DMARDs typically begin working around 2–3 months after starting the medication. In contrast, the ACR guidelines do not recommend glucocorticoids [14,16]. Notably, only approximately 30% of patients achieve remission with methotrexate monotherapy [49].

Remission criteria include Boolean 2.0 remission, a Simplified Disease Activity Index (SDAI) score of ≤ 3.3 and a Clinical Disease Activity Index (CDAI) score of ≤ 2.8 and Disease Activity Score in 28 joints (DAS28). In Boolean 2.0 criteria, remission is defined as a tender joint count ≤ 1, swollen joint count ≤ 1, C-reactive protein ≤ 1 mg/dL, and a patient global assessment ≤ 2 (on a 0–10 scale) [15]. The DAS28 score, which is commonly used to assess disease activity objectively, is calculated based on the number of tender and swollen joints (out of 28 specified joints), the erythrocyte sedimentation rate, and the patient's assessment of disease activity using a specific formula. DAS28 scores are interpreted as: > 5.1 indicates high disease activity, 3.2–5.1 represents moderate activity, < 3.2 indicates low activity, and < 2.6 signifies remission [5].

In cases of methotrexate treatment failure, EULAR recommends using other conventional synthetic DMARDs (leflunomide or sulfasalazine) in patients without poor prognostic factors. These factors include high disease activity, a high swollen joint count, failure to respond to two csDMARDs, elevated acute phase reactant levels, the presence of autoantibodies and early erosions. For patients with poor prognostic factors, a biological or targeted synthetic DMARD should be added to the conventional synthetic DMARD therapy.

When bDMARD therapy is used, glucocorticoids should be stopped, as their combination extends the therapy and is associated with more adverse events, mainly infections. The ACR guidelines recommend adding a bDMARD or tsDMARD to methotrexate instead of more csDMARDs, other than patients with a history of serious infections or non-tuberculous mycobacterial lung disease, where adding csDMARDs is suggested.

Monitoring of active disease should occur every 1–3 months. If this therapy does not achieve adequate disease control within 3-6 months, treatment should be modified. In cases where the first bDMARD or tsDMARD is ineffective, guidelines recommend using another bDMARD (from a different or the same class) or another tsDMARD [14,16].

In patients who achieve sustained remission after 6 months, the dose reduction may be considered, but complete discontinuation is not recommended. Several studies show that tapering disease-modifying antirheumatic drugs results in lower rates of flare-free survival compared with those continuing csDMARD treatment [50].

5. Treatment of Difficult-to-treat Rheumatoid Arthritis

The advent of bDMARDs and tsDMARDs has substantially improved outcomes for many patients. Nevertheless, a subgroup of patients classified as having difficult-to-treat (D2T) RA persists, with an estimated prevalence ranging from 5–20% [51].

The European Alliance of Associations for Rheumatology (EULAR) defines difficult-to-treat rheumatoid arthritis based on the following criteria:

- Failure of treatment with at least two bDMARDs or tsDMARDs with different mechanisms of action in patients with RA refractory to conventional synthetic DMARDs.
- At least moderate disease activity, with clinical signs and symptoms indicating active disease, inability to taper glucocorticoids below 7.5 mg/day of prednisone or equivalent, imaging evidence of disease progression, or RA-related impairment in quality of life.
- RA-related symptoms perceived as problematic by rheumatologists or the patients [52].

The causes of DMARD inefficacy in difficult-to-treat RA remain incompletely understood. Factors associated with difficult-to-treat rheumatoid arthritis (D2T RA) include comorbidities, low socioeconomic

status, altered pain processing, smoking, and a sedentary lifestyle. Some studies suggest the involvement of immunological and molecular mechanisms such as increased Th17 cells, activated memory B cells (CD95+ Ki67), synovial lymphoid aggregates, and epigenetic predispositions [53].

For difficult-to-treat rheumatoid arthritis, management involves reassessing the RA diagnosis, addressing issues related to treatment non-adherence, optimizing the management and exploring non-drug interventions and self-management programs. Additional diagnostic tests should be considered for symptoms. Other non-pharmacological interventions, including patient education programs, have demonstrated benefit such as function, pain, and fatigue.

JAK inhibitors such as upadacitinib and filgotinib remain effective in patients with difficult-to-treat RA, regardless of prior treatments. However, their effectiveness tends to diminish in patients who have failed multiple bDMARD therapies [54].

6. Discussion

Pharmacological treatment is enabling effective control of disease activity, reduction of pain and inflammation, and prevention of structural joint damage. Early diagnosis and timely initiation of therapy are essential for improving clinical outcomes and quality of life.

csDMARDs, particularly methotrexate, remain the first-line therapy for most patients. However, a substantial proportion of individuals do not achieve remission with csDMARD monotherapy or experience adverse effects. The introduction of biological and targeted synthetic DMARDs has significantly expanded therapeutic options, making remission or low disease activity an achievable goal for many patients.

Clinical evidence confirms that bDMARDs and tsDMARDs effectively reduce disease activity and slow radiographic progression. Nevertheless, variability in treatment response and concerns regarding long-term safety highlight the importance of individualized treatment strategies, careful monitoring, and continued research.

7. Conclusions

Pharmacological therapy plays a central role in the management of rheumatoid arthritis. The use of disease-modifying antirheumatic drugs, particularly biological and targeted synthetic agents, has substantially improved disease control and quality of life. Individualized treatment approaches that consider disease activity and drug safety are essential for optimal outcomes. Despite significant progress, further research is required to better characterize long-term safety and to develop more effective and safer therapeutic strategies for patients with rheumatoid arthritis.

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