



## Rheumatoid Arthritis: Modern Pharmacologic Therapies: Review Article

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### ABSTRACT

Rheumatoid arthritis (RA) is a long-term autoimmune condition that causes pain, inflammation, and impairment in the joints. An outline of the pathogenesis, clinical characteristics, and available treatments for RA is given in this review. Traditional synthetic disease-modifying antirheumatic medicines (DMARDs), biologic DMARDs, and more recent pharmaceuticals are used in its treatment. Targeted treatments, such as TNF- $\alpha$  and IL-6 inhibitors, have been developed as a result of recent developments in our understanding of the pathophysiology of RA. The goal of this review is to present a thorough update on managing RA, emphasizing the most recent available treatments and current research in the area.

**Key words:** rheumatoid arthritis, DMARDs, BDMARDs, TNF- $\alpha$  inhibitors, IL-6 inhibitors

### Introduction

The chronic systemic condition known as rheumatoid arthritis is more common in women than in men. The lining of the synovial joints is the main target of rheumatoid arthritis, which can lead to increasing impairment. In addition to frequently causing harm to several organs, RA invariably results in irreparable damage to the structural joints. Deformed joints result in irreversible physical impairment, and joint degeneration advances in the early stages following commencement.



Figure 1

Small joints are first affected by rheumatoid arthritis, which then spreads to larger joints and, ultimately, the skin, eyes, heart, kidney, and lungs. Tendons and ligaments deteriorate, and joint bone and cartilage are frequently damaged. All of this joint deterioration results in deformity and bone erosion, which are typically extremely painful for the patient. Morning stiffness of the affected joint for more than half an hour is one of the prevalent symptoms of RA.

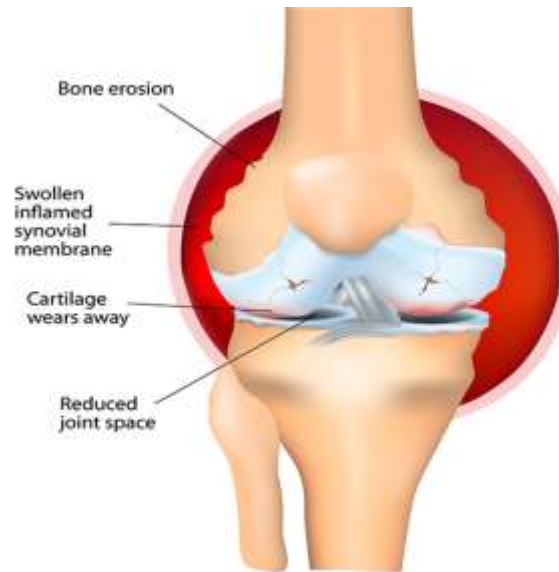


Figure 2

## Pathogenesis

The presence or lack of anti-citrullinated protein antibodies (ACPAs) distinguishes the two main subtypes of RA. The calcium-dependent enzyme peptidyl-arginine-deiminase (PAD) catalyzes the process of citrullination, which results in a polar but neutral citrulline as a result of a post-translational modification. Approximately 67% of RA patients have ACPAs, which are a useful diagnostic reference for patients with early, undifferentiated arthritis and provide an indication of likely disease progression through to RA. The clinical phenotypes of RA that is more aggressive than the ACPA-negative subset exhibits distinct genetic association patterns and immune cell responses to citrullinated antigens. In terms of treatment, the ACPA-negative fraction showed a less effective response to rituximab or methotrexate (MTX). This implies that further research on possible pathophysiological differences between these two categories is necessary. We will categorize the RA process into multiple separate stages and concentrate on the ACPA-positive subset of RA for the purposes of this review. It is important to note, though, that these phases could happen one after the other or all at once.

## Clinical features

### Signs and symptoms

fatigue, tightness in the morning, fever, Loss of weight, tender joints, Warm and swollen, Under-skin rheumatoid nodules The solution to this illness typically occurs between the ages of 35 and 60.

Additionally, it can affect young children before they turn 16.

### RA begins prior to the appearance of clinically apparent IA

Generally speaking, it seems that the natural history of RA starts before clinical RA, or "pre-RA," when environmental and genetic factors combine to cause early lapses in immunological tolerance.

Although several other antibodies, such as anti-carbamylated protein (anti-CarP), anti-malondialdehyde-acetaldehyde (anti-MAA), and anti-peptidyl arginine deiminase (anti-PAD) antibodies, have been identified, rheumatoid arthritis has been best identified by blood elevation of antibodies such as RF and ACPA. On average, these antibodies are raised three to five years before a clinical RA diagnosis.

### Predicting future clinical RA

In order to identify people who are at a high risk of developing clinical RA, numerous prospective studies have attempted to develop prediction strategies. The most well-researched indicator of RA risk is autoantibodies. Other blood-based bio markers, including cytokines, chemokines, and cell subsets, have also been explored in RA prediction.

## MODERN RA PHARMACOLOGIC THERAPIES

Symptomatic management and disease modification are the current treatment tenets for established RA.

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## Conventional synthetic DMARDs (CS DMARDs)

### Methotrexate

Oral MTX has a more variable uptake than subcutaneous administration, which also leads to fewer significant side effects. MTX is the cornerstone in the treatment of RA, either as a single agent or in combination with other DMARDs. However, its use was associated with a 16% discontinuation rate due to adverse side effects. MTX is administered as a low-dose (5 to 25 mg) weekly regimen with dosing conditional to the disease state and side effect.

### Sulfasalazine (SSZ)

Possessing clinical trials SSZ's anti-inflammatory and anti-microbial properties have made it a popular treatment drug for RA. 5-amino salicylic acid (5-ASA) and sulphapyridine are its metabolites. By modulating the receptor activator of nuclear factor  $\kappa$ B rank, SSZ can decrease osteoclast development and boost adenosine synthesis at the site of inflammation. Megaloblastic anemia, oligospermia, rash, liver dysfunction, leukopenia and agranulocytosis, gastrointestinal and central nervous system toxicity, and infertility are among the main side effects of SSZ.

### Hydroxychloroquine

Hydroxychloroquine is intended to reduce the generation of pro-inflammatory cytokines and disrupt the interaction between antigen-presenting macrophages and T helper cells that lead to joint inflammation in RA, hence lowering the overall inflammatory response. By affecting intracellular TLRs, especially TLR9, preventing TNF synthesis, and obstructing the translation of membrane-bound Pro-TNF into soluble mature protein, it also seems to function independently of lysosomes.

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## Biological DMARDs (BDMARDs)-TNF- $\alpha$ inhibitor (TNFi)

### Infliximab (IFX)

T cells, T lymphocytes, and activated monocytes all release TNF- $\alpha$ , which sets up inflammatory reactions. TNF- $\alpha$  functions via TNF receptors 1 and 2, each of which has a distinct affinity for TNF- $\alpha$  and some species specificity. Because inflammatory musculoskeletal illnesses have elevated TNF- $\alpha$  levels, it has been suggested that TNF- $\alpha$  mediates local bone degradation in these conditions. The first TNFi for the treatment of RA was infliximab (IFX), which is a recombinant chimeric monoclonal antibody made up of a mouse idiotype and a human antibody backbone. The adhesion molecule decreased following IFX treatment for RA. MCP-1, IL-1, IL-6, and IL-8 were detected. Additionally, the thickness of the synovial lining layer was determined.

### Adalimumab

A fully humanized anti-TNF monoclonal antibody with a less noticeable adverse profile, adalimumab (Ada) is administered subcutaneously every two weeks.

### IL-6 inhibition

#### Tocilizumab (TCZ)

A humanized monoclonal antibody called tocilizumab (TCZ) targets the circulating and cell-surface IL-6 receptor. Numerous cell types, such as T cells, B cells, monocytes, fibroblasts, endothelial cells, and synovial cells, generate IL-6. mL-6R (CD 126) and sIL-6R are its two receptors. There are intravenous and subcutaneous forms of TCZ. It poses little risk of immunogenicity. It offers yet another worthwhile opportunity to investigate the role of cytokine inhibition, as opposed to cytokine receptor inhibition, in RA. Nasopharyngitis and upper respiratory tract infections were the most frequent side effects seen in clinical trials. Adalimumab, a TNF-targeting medication, has been shown to be just as effective in treating MTX-refractory RA as the newest IL-6 receptor-targeting medication among the nine BDMARDs. Tocilizumab and sarilumab are currently undergoing clinical trials to treat cytokine release syndrome linked to the novel coronavirus illness 2019 (COVID-19).

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## Newer Medications

### Leflunomide

Oral leflunomide suppresses the formation of ribonucleotide uridine monophosphate pyrimidine by converting to malononitrilamide. It reduces RA's symptoms and slows its progression.

### Anakinra

Anakinra is a medication administered subcutaneously once a day. It functions by attaching itself to the molecular transmitter of inflammation, IL-1. It can be used as a monotherapy or in conjunction with other DMARDs, however it is not as commonly utilized as other biologics because of its poor response rate.

### Surgery

The 1990s saw a high in RA patients undergoing joint surgery. Nonetheless, a 2010 study found that fewer RA patients aged 40 to 59 had joint surgery. As a last option, surgery is used to treat RA. Repairing a recent tendon rupture, usually in the hand, or excising inflammatory tendon sheaths are both part of a tenosynovectomy. A less expensive option to surgical synovectomy is radiosynovectomy, which treats several joints at once by injecting tiny radioactive particles intra-articularly.

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## Conclusion

To sum up, RA is a complicated, multifaceted autoimmune condition that necessitates an all-encompassing approach to treatment. The creation of biologic DMARDs, such as IL-6 and TNF-alpha inhibitors, has transformed the way RA is treated and given patients better results and a higher quality of life. In the end, attaining ideal disease control and enhancing patient well-being requires a customized and multidisciplinary approach to RA care that includes lifestyle changes, medication interventions, and continuous monitoring.

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