



# REVOLUTIONARY TREATMENT STRATEGIES FOR RHEUMATOID ARTHRITIS

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## ABSTRACT

Rheumatoid arthritis is a chronic autoimmune condition that affects about 1% of the population and typically manifests between the ages of 30 and 50. Over the past 25 years, there has been a significant shift in the goals and outcomes of RA treatment, partly due to a better understanding of the disease's pathophysiology. The prevalence of rheumatoid arthritis in adult U.S. was estimated to be 1.29 million (0.6%) using data between 1995 and 2005, down from the prior estimate of 2.1 million. Age significantly increased the prevalence of RA in men and increased it in women. Leukocyte infiltration into the synovium is what causes synovitis. Inflammation results from the secretion of the cytokines transforming growth factor, interleukin (IL)-1, IL-6, IL-21, and IL-23 by dendritic cells and macrophages, which promote the development of Th17 cells and restrict the generation of regulatory T cells. Multiple potential strategies may be used to mediate the role of B cells in autoimmune illness. Multiple joints are frequently painful and stiff in RA patients. Inflammatory etiology may be the cause of morning stiffness lasting longer than an hour. Imaging techniques such as color, Doppler sonography or Gadolinium-enhanced magnetic resonance imaging can detect the presence of tenosynovitis. Leflunomide is a DMARD that primarily targets lymphocytes by preventing the synthesis of pyrimidine. It produces similar improvements in clinical measurements and radiographic scores as methotrexate when used as a monotherapy. When side effects prevent its usage, it is frequently combined with other DMARDs such as cholestyramine for quick drug removals. The immune system mistakenly views bodily cells as alien substances in autoimmune illnesses like rheumatoid arthritis. Mesenchymal stem cells (MSCs) contain immunomodulatory characteristics, which allow them to alter the immune response. MSCs may lessen inflammation in troubled joints by reducing or suppressing the immune system. All-arthroplasty is more common in arthritis than a standard operation. Hip and knee replacements are frequently required on the equal side. Arthrodesis became a

common treatment for wrist arthritis. For the proximal interphalangeal and metacarpophalangeal joint, surgery is still the gold standard.

**KEYWORDS:** Rheumatoid arthritis, autoimmune mechanisms, interleukin, color doppler sonography, Leflunomide, Mesenchymal stem cell.

## Introduction

Rheumatoid arthritis is a chronic autoimmune condition that classically presents as a symmetrical polyarthritis of proximal small synovial joints<sup>1</sup>. RA that is left untreated can result in progressive joint degeneration, which can cause disability, poor quality of life, and a higher mortality rate. With a higher frequency in women, the condition affects about 1% of the population and typically manifests between the ages of 30 and 50<sup>2</sup>. Despite significant progress in the past 20 years, the pathological processes underlying rheumatoid arthritis remain poorly understood. Over the past 25 years, there has been a significant shift in the goals and outcomes of RA treatment, partly due to a better understanding of the disease's pathophysiology. The primary method of treatment for rheumatoid arthritis according to worldwide guidelines is DMARDs, such as methotrexate, with biologic DMARDs often only being used when the former is ineffective<sup>3</sup>. In the first half of the 20th century, RA treatment plans comprised analgesics, salicylates—from which NSAIDs were derived drugs that could only treat symptoms as well as physical interventions including bed rest, splinting, and physical therapy. There are numerous pro-inflammatory cytokines involved, some of which are potential therapeutic targets for the creation of novel medications<sup>4</sup>. For the first time, Rheumatologists got access to medications that they believed would have a significant impact on disease activity. Later, these treatments were broadened to include additional medications (such as parenteral gold salts, SSZ, chloroquine, HCQ, D-Pen, ciclosporin, and AZA), which were optimistically referred to as DMARDs. The pyramidal approach to treating patients with newly diagnosed RA was advised it involved starting with analgesics, moving on to NSAIDs, and finishing with DMARDs. This method improved some—but not all—RA patients, with fewer symptoms and, in some cases, lower disease activity. However, there was initially a lack of large early clinical trials demonstrating DMARD reduction in the course of structural joint degeneration<sup>6</sup>. Gout, once known as the "disease of kings and king of diseases," is among the most prevalent etiologies of chronic inflammatory arthritis in the United States, characterized by monosodium urate (MSU) monohydrate crystals deposition in the tissues. Gout is the most common form of inflammatory arthritis, with a prevalence of 3.9% in the United States, affecting 8.3 million adults<sup>5</sup>. In this review we discuss the updated treatment of Rheumatoid Arthritis.

## Epidemiology

Studies on the prevalence of rheumatoid arthritis are scarce. This almost certainly reflects both its relative rarity in the population and the challenge of accurately identifying every case when it arises. The most reliable information comes from recent research conducted in the United Kingdom, where efforts were made to keep track of all inflammatory arthritis cases that presented to primary care<sup>7</sup>. At the time of presentation between 1990 and 1991, 104 newly diagnosed cases of RA were found that met the 1987

American College of Rheumatology (ACR) criteria for RA. In men under 45, RA was uncommon. Age significantly increased the prevalence of RA in men. Up until the age of 45, the incidence in women increased. It then stopped growing until the age of 75, at which point it started to fall. The estimation of the incidence of RA in 1990 was investigated by the same researchers in a subsequent publication by allowing each condition to "carry forward" after it had been met once<sup>8</sup>. The prevalence of RA in adult Americans was estimated to be 1.29 million (0.6%) using data between 1995 and 2005, down from the prior estimate of 2.1 million. In 1995, there were 1.06 per cent more American women who had RA than there were men (0.61%). Interestingly, considering the majority of the data came from Midwestern U.S patients, they might not apply to others other than North American<sup>9</sup>. As part of self-care, it's crucial to lessen the stress in your life because, according to research, stress can make symptoms of rheumatoid arthritis worse.

### Diagram

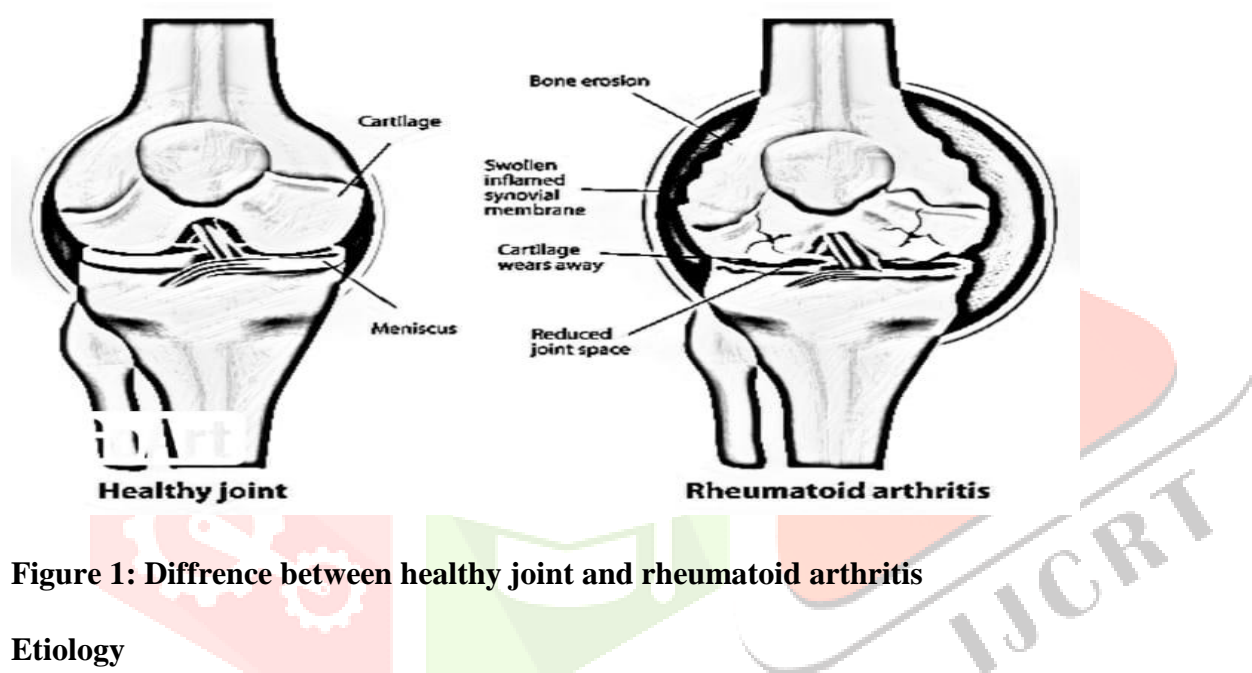


Figure 1: Difference between healthy joint and rheumatoid arthritis

### Etiology

INFECTIOUS AGENT	POTENTIAL PATHOGENEICMECHANISM
Mycoplasma	Direct synovial infection; superantigens
Parvovirus B19	Direct synovial infection
Retrovirus	Direct synovial infection
Enteric Bacteria	Molecular mimicry(QKRAA,e.g, in bacterial heat shock proteins)
Mycobacterium	Molecular mimicry (proteoglycans QKRAA), immunostimulatory DNA(toll-like receptor 9 activations)
Epstein-Barr virus	Molecular mimicry(QKRAA in GP 110 )
Bacterial Cell wall	Toll-like receptor 9 activation

Table 1: Infectious agent and potential pathogenetic mechanism

## Smoking and Other Airborne Exposures

The most significant of these exposures is smoking, which has been identified as one of the major risk factors for the onset of RA. A clear dose-response relationship also exists, with current or heavy smokers having substantially higher risks than former or light smokers, respectively, and a linear increase in risk with pack-years of smoking<sup>13,14</sup>. Therefore, it has been demonstrated that quitting smoking gradually reduces the risk of developing RA, returning to that of never smokers over a 20–30 year period<sup>13</sup>.

## Environmental Factors

Airborne exposures, particularly smoking, microbiota and pathogenic agents, food, and socioeconomic factors, including occupational and recreational exposures, can be loosely divided into four categories. There is a wealth of information that directly links these many factors to the aetiology of RA. Evidence suggests that major environmental factors for RA may take effect years before symptoms of the disease are visible. Even though autoimmune disorders tend to affect adults more frequently, they can also affect children. Very young children can develop RA and SLE, which lends support to the idea that significant environmental variables must exist at or before this period. In addition, adult RA immunological pathology starts years before the onset of clinical disease. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), two autoantibodies linked to RA, may be present more than 10 years before the development of clinical disease.

## Diet

There has been a lot of research on the epidemiological relationship between dietary variables and RA. Despite the challenges in precisely determining patient nutritional behaviour before the development of RA and determining the impact of a specific food, beverage, or vitamin, some results are reliable. Importantly, they also offer insights into the pathogenesis and aetiology of RA, as demonstrated by the effect that diet has on altering the gut microbiota and RA risk<sup>14,15</sup>. Alcohol use that is mild to moderate is preventive of the onset of RA. A balanced diet must include fruits and vegetables since they are a primary source of fibre and anti-inflammatory nutrients like vitamin C. Both have been linked to a lower risk of RA<sup>16,17</sup>.

## Pathogenesis

Damage to the joints caused by synovitis, swelling, and active RA is characterised by the findings of complex inflammatory and autoimmune mechanisms that both innate and adaptive immune system components systems<sup>10</sup>. Patients with common epitopes produce citrullinated peptides that the immune system no longer recognises as "self," causing ACPAs to form against them<sup>11</sup>. Leukocyte infiltration into the synovium is what causes synovitis. Instead of local cellular proliferation, leukocyte migration from distant sites of creation in response to the production of adhesion molecules and chemokines by activated endothelial cells of synovial microvessels causes the accumulation of leukocytes in the synovium. The development of RA illness and immunological activation is a complicated process that involves interactions between elements of the innate and adaptive immune systems. The local cytokine and chemokine milieu of

the synovium where these interactions occur has a significant impact on the nature of those interactions<sup>10</sup>. The presence of dendritic cells, a significant class of antigen-presenting cells that express several cytokines, HLA class II molecules, and costimulatory molecules near T cell clusters in the synovium, suggests the significance of the adaptive immunological response in RA. T cells present in the synovium are given antigens by dendritic cells, which are also a step in the activation of T cells<sup>18</sup>. Native T helper (Th) cells differentiate into three main subpopulations (Th1, Th2, and Th17) with diverse cytokine production patterns and functions when T-cell activation does occur. Although Th1 cells have long been thought to have a role in the pathogenesis of RA, recent research has focused on the Th17 subpopulation. Inflammation results from the secretion of the cytokines transforming growth factor- $\beta$ , interleukin (IL)-1, IL-6, IL-21, and IL-23 by dendritic cells and macrophages, which promote the development of Th17 cells and restrict the generation of regulatory T cells<sup>10</sup>. Additionally essential to the pathophysiology of RA is humoral adaptive immunity. Multiple potential strategies may be used to mediate the role of B cells in autoimmune illness. Autoreactive B cells, which function as antigen-presenting cells and are capable of activating T cells, can be the result of defects in B-cell tolerance checkpoints. Additionally, pro- and anti-inflammatory cytokines can be produced by B cells. Finally, B cells can operate as cells that make antibodies. These mechanisms may contribute to RA pathogenesis singly or in combination<sup>19</sup>.

## Diagnosis

### Typical presentation

Multiple joints are frequently painful and stiff in RA patients. The most frequently affected joints are the wrists, proximal interphalangeal joints, and metacarpophalangeal joints. Inflammatory aetiology may be the cause of morning stiffness lasting longer than an hour. On joint inspection, modest synovial thickening or bog-like oedema caused by synovitis may be palpable. Before the beginning of clinically obvious joint swelling, patients may sometimes present with more subdued arthralgias. With active illnesses, systemic signs like weariness, weight loss, and low-grade fever could appear.

Early on in the disease, RA may only affect one or a few joints. Tenosynovitis, an inflammation of the tendon, appears concurrently or even earlier. Imaging techniques such as colour Doppler sonography or Gadolinium-enhanced magnetic resonance imaging can detect the presence of tenosynovitis, such as at the flexor carpi ulnaris tendon, and subclinical synovial inflammation by demonstrating expansion of intra-articular soft tissue or hypervascularization of the synovial membrane. There are no diagnostic standards for RA. However, although being created for the identification of homogenous patient populations in clinical investigations of RA, the 2010 categorization criteria may assist medical professionals in making a diagnosis<sup>20,21</sup>.

At least one clinically swollen joint must be present, and a scoring system must yield at least 6 out of 10 points for the condition to be classified as RA<sup>22</sup>. Up to 5 points are awarded for joint involvement determined by physical examination, imaging with ultrasound or magnetic resonance imaging, elevated levels of RF or ACPAs, or both; elevated acute phase reactant (APR) response, such as an elevated CRP



level or erythrocyte sedimentation rate; and duration of symptoms (6 weeks) each award an additional point. The sensitivity and specificity of these 2010 criteria are 82% and 61%, respectively. In comparison to the 1987 criteria, the new classification criterion's sensitivity was 11% higher and its specificity was 4% lower<sup>23</sup>.

Since 90% of people with early RA are prevented from developing joint degeneration by early identification and therapy<sup>24</sup>. Recognizing RA patients as soon as feasible is crucial. Specific signs and symptoms of RA include autoantibody-positive, morning stiffness of the fingers lasting 30 minutes or longer, and articular discomfort and oedema in the metacarpophalangeal joints, metatarsophalangeal joints, or both<sup>25</sup>.

### **Differential diagnosis**

Skin abnormalities may indicate systemic lupus erythematosus, systemic sclerosis, or psoriatic arthritis. An older patient with symptoms mostly in the shoulder and hip should be evaluated for polymyalgia rheumatic, and the patient should be questioned about any accompanying temporal arteritis. Chest radiography is useful in determining whether sarcoidosis is the cause of arthritis. Spondyloarthropathy can affect those who have inflammatory back symptoms, a history of inflammatory bowel illness, or inflammatory eye disease. People who have symptoms for less than six weeks may be suffering from a viral condition like parvovirus. Repeated episodes of acute joint swelling that go away on their own suggest crystal arthropathy, so an arthrocentesis should be done to check for calcium pyrophosphate or monosodium urate crystals<sup>20,27</sup>.

### **Diagnostic tests:**

Antinuclear antibody testing can be positive in RA patients, and it's important for predicting outcomes in children with the disease<sup>26</sup>. With active RA, erythrocyte sedimentation rate and C-reactive protein levels are frequently elevated, and these acute phase reactants are part of the revised RA categorization criteria<sup>22</sup>. RA radiographic indicators like joint space later on in the process, narrowing, erosions, and subluxation occur. The prevalent technique in plain radiography determines the degree of anatomical alterations in RA patients. However, there are not many statistics on the worth of recent-onset cases, standard radiography examination arthritis. The first radiological sign may be juxta-articular osteoporosis characteristics of the hand joints in early RA.<sup>27</sup> These results are typical with synovitis, however not seen on standard radiographs in all patients. They are unreliable in the sense that they lack sufficient precision routine evaluation of synovitis<sup>28</sup>. Sonography is a reliable technique that detects more erosion than radiography, especially in early RA<sup>29</sup>. The development of MRI imaging offers further information diagnostic centres for RA early diagnosis and separating RA from diseases that are not RA. MRI results may more people with genuine RA can be found as compared to ACR diagnostic criteria<sup>30</sup>.

## Treatment

### Initial treatment

Methotrexate, a common synthetic DMARD, should be used in the routine initial treatment after the diagnosis of rheumatoid arthritis if it is not contraindicated<sup>31,32</sup>. However, the inclusion of biological DMARDs or Janus kinase (JAK) inhibitors is advised when no improvement is seen within 3 months or when no remission is established within 6 months, despite a rise to the full dose of methotrexate. Approximately 3-6 months later, biological DMARDs or JAK inhibitors should be changed if the treatment objective is still not met. Glucocorticoids are advised for short-term usage for up to 3 months as an adjuvant therapy to reduce pain and oedema when arthritis first manifests or recurs.

### Methotrexate(MTX)

Unlike targeted DMARDs, conventional synthetic DMARDs came into clinical practice based on empiric observations and their mechanisms of action are still incompletely understood<sup>32</sup>. High-dose methotrexate's method of action is well-known to involve the depletion of thymidine and purine residues as well as cell-cycle arrest at S1. Although folate co-therapy does not cause a reduction in the therapeutic benefit, this mechanism does not appear to be a significant factor in the clinical effect of low-dose MTX. The pleiotropic therapeutic effects of methotrexate on different immune cells and mediators lead to a general slowing of the inflammatory response. Low-dose MTX is believed to primarily treat rheumatoid arthritis via potentiating adenosine signalling. Through four different purinergic G-protein-coupled receptors, which are overexpressed in rheumatoid arthritis, adenosine functions as a paracrine signalling agent. Adenosine may be one of the primary mediators of the downregulation of the activation and proliferation of T-lymphocytes, resulting in the creation of an immunotolerant environment, in addition to downregulating the production of tumour necrosis factor (TNF) and NF- $\kappa$ B<sup>33</sup>.

### Sulfasalazine

In 1938, sulfasalazine SSZ was created specifically to treat rheumatoid arthritis. The drug's formulation was intended to combine antibacterial and anti-inflammatory properties. Rheumatoid arthritis can be effectively treated with sulfasalazine, but its exact mechanism of action is yet unknown. The gut bacterial flora, inflammatory cell activities, and immunological processes are among the key pharmacological actions of SSZ<sup>34</sup>.

Sulfasalazine frequently causes adverse reactions, including idiosyncratic (such as hypersensitivity-immune-related) and dose-related effects. These include adverse effects on the gastrointestinal tract, the central nervous system, the skin, and the hematologic system. The withdrawal rate for adverse events is around 25%, and toxicity to the gastrointestinal and central neurological systems accounts for two-thirds of these withdrawals. If there are dose-related side effects, medication can be stopped for a week, and then resumed at a lower dose once the symptoms have subsided<sup>35</sup>.

Sulfasalazine can typically be used after surgery because it only has a short half-life of 4-5 hours and a negligible immunosuppressive effect. Sulfasalazine can be stopped on the day of surgery if there is a chance of an interaction or a potential additive hepatotoxic impact with medicine used before surgery<sup>36</sup>.

### **Leflunomide**

Leflunomide is a DMARD that primarily targets lymphocytes by preventing the synthesis of pyrimidine. It produces similar improvements in clinical measurements and radiographic scores as methotrexate when used as a monotherapy. When the side effects of methotrexate prevent its usage, it is frequently combined with other DMARDs or biologic DMARDs in place of methotrexate. Similar to methotrexate, Leflunomide should not be used if there is an active infection, pre-existing liver illness, alcoholism, pregnancy (or insufficient contraception), or any of these conditions. Leflunomide can be administered to patients with mild to moderate renal impairment, unlike methotrexate. Leflunomide's prolonged half-life as a result of plasma protein binding and enterohepatic circulation makes it special. Therefore, when conditions call for quick drug removals, such as during acute illnesses or pregnancy, an elimination strategy involving cholestyramine is frequently required<sup>37</sup>.

### **TNF alpha inhibitor**

#### **Adalimumab**

Adalimumab is the first fully human monoclonal antibody that binds TNF. It is administered subcutaneously and has a slightly longer half-life than etanercept (about 13 days), enabling less frequent injection intervals (every two weeks). Clinically useful combinations of adalimumab and methotrexate have been shown to help patients with early-onset, active rheumatoid arthritis<sup>38</sup>. In a recent study, patients who had attained a low disease activity state with the combination after 24 weeks were re-randomized. The study assessed the use of methotrexate + adalimumab as first-line treatment for individuals with early rheumatoid arthritis. 90% of patients who stayed on both medications for the full 76 weeks (compared to 80% of those who persisted on methotrexate alone) had sustained low disease activity (disease activity score [DAS]  $28 > 3.2$ ). Even while this difference was statistically significant, the most relevant finding may be that induction maintenance is a highly effective therapeutic approach with an unmistakably positive health economic profile for at least a portion of patients with early rheumatoid arthritis.

#### **Anakinra**

Anakinra, a recombinant human IL-1 receptor antagonist, is to be given subcutaneously once a day and has a very short half-life (4-6 hours). Due to this drawback, as well as indirect comparisons reveal anakinra's low effectiveness in treating rheumatoid arthritis in comparison to TNF inhibitors.<sup>39</sup> In adult rheumatoid arthritis, this medication is not frequently prescribed. However, anakinra has been used to treat juvenile rheumatoid arthritis and other autoinflammatory diseases with success<sup>40</sup>.



## Interleukin 1

There are three members of the IL-1 family: IL-1, which is responsible for the biological effects attributed to this cytokine, and IL-1 receptor antagonist (IL-1Ra), an endogenous inhibitor that prevents the other two members from acting. Despite having similar three-dimensional shapes, each member of the family has a unique amino acid sequence. Pro-IL-1 and pro-IL-1, the precursor proteins for IL-1 and IL-1 that are created, are 31 kDa proteins that are later broken down into the mature 17 kDa protein by cellular proteases. Since IL-1 is typically kept inside cells or expressed on the cell surface, it is thought to work as an autocrine messenger. Contrarily, IL-1 is released and exerts its biological effects by interfering with other cells. The same cells that express IL-1 also produce and secrete IL-1Ra, a protein with a 17 kDa molecular weight. Additionally, numerous intracellular IL-1Ra variants have been discovered; as a result, these may play a greater role in controlling the autocrine activities of IL-1. Because the type II IL-1 receptors (IL-1RII) on these cells have a relatively short cytoplasmic domain that is unable to transmit signals after IL-1 binding, binding to these receptors does not result in cell activation. IL-1RII acts as a sham receptor as a result. As its name suggests, IL-1Ra binds to both IL-1RI and IL-1RII but does not cause signal transduction. Instead, it inhibits IL-1 and IL-1 binding by competitive antagonism, lessening the biological effects of these cytokines<sup>41</sup>.

## Interleukin 4

the ability of IL-4 to reduce inflammation. According to some studies, IL-4 is not required for disease, but other research suggests that IL-4 deficiency can lower arthritis levels. In RA, IL-4 insufficiency lowers the level of pathogenic autoantibodies, which slows the development of arthritis<sup>42</sup>.

## New anti-rheumatic agents

New cytokine-targeting medications include those against IL-17 and IL-15. Many rheumatoid arthritis patients have high serum and, to a greater extent, synovial fluid IL-17A levels, which are linked to cartilage and bone deterioration. Phase II clinical trials have assessed the anti-IL-17A monoclonal antibodies secukinumab, ixekizumab, and brodalumab as well as the anti-IL-17 receptor subunit A monoclonal antibody. Secukinumab is the most developed of these, with phase III trials being conducted in patients who had a poor response to prior TNF-blocker medication<sup>43</sup>.

IL-20 has also been discovered to be involved in the aetiology of rheumatoid arthritis. Patients with rheumatoid arthritis have synoviums that are higher in this cytokine. Phase II trials are now taking place for NNC0109-0012, a human recombinant IgG4 that binds and neutralises IL-20. Especially in patients with seropositive rheumatoid arthritis, a double-blind study's results showed considerable improvements in disease activity ratings, physical function, and discomfort<sup>44</sup>.

## JAK inhibitors in rheumatoid arthritis

The first JAK inhibitor created and introduced to the market for the treatment of RA was tofacitinib. A collaborative public-private partnership between the National Institutes of Health (NIH) and Pfizer began working on its development in the middle of the 1990s. Baricitinib is a JAK1/JAK2 inhibitor with moderate activity against TYK2 and minimal activity against JAK3. To only affect the JAK1 pathway, upadacitinib is used. The reasoning behind this is that more targeted JAK inhibition may lessen dose-related toxicity and adverse effects without significantly reducing efficacy. HLA-DRB1 had the strongest correlation among disease-susceptibility genes including PTPN22, CTLA4, and STAT4 in genome-wide association studies (GWAS) of SNPs in patients with RA. Anti-citrullinated protein antibodies are produced in response to HLA-DRB1 alleles, which encode protein chains with the same epitope motif. Despite the lack of a known specific autoantigen, the interaction of genetic and environmental factors, as well as citrullination of extracellular matrix molecules like fibrinogen and filaggrin, induces autoimmunity in RA through epigenetic modification and conformational changes that impair immune tolerance to antigens. Angiogenesis, vasodilation, and synovial cell proliferation come from the accumulation of autoreactive T and B lymphocytes in synovial tissue. Additionally, rheumatoid synovial fibroblasts overproduce pro-inflammatory cytokines, primarily IL-6. Numerous cytokines, such as IL-6, interferons, and GM-CSF, are direct targets for JAK inhibitors based on the nature of these and other pathogenic processes in RA, while the production of other cytokines, such as TNF, might be indirectly impacted<sup>45</sup>.

## Stem cell therapy in rheumatoid arthritis

The FDA has not yet approved stem cell therapy as a RA therapeutic option. Mesenchymal stem cells (MSCs) are increasingly being investigated in RA patients, nevertheless. The immune system mistakenly views bodily cells as alien substances in autoimmune illnesses like RA, leading to the production of cells that attack healthy tissue. The tissue that creates the fluid that lubricates joints, the synovium, is attacked by the immune system in rheumatoid arthritis. Inflammation, joint discomfort, stiffness, and oedema are all symptoms of damaged tissue. MSCs contain immunomodulatory characteristics, which allow them to alter the immune response. MSCs may lessen inflammation in troubled joints by reducing or suppressing the immune system. By lowering immune cell counts or activity as well as the particular inflammatory chemicals they secrete, MSCs suppress the immunological response<sup>46</sup>.

## Surgical treatment

However, it is unknown how well these treatments will work in the long run. Changes in scores are typically used to quantify structural damage in RA. Radiography of the hands or feet is used. Larger joints should not routinely undergo serial radiography generally accessible. While the degree of inflammation in RA might change over time, structural damage is a cumulative process that cannot be stopped<sup>47</sup>. Orthopaedic surgery is essential in managing joint degeneration because it can rectify deformities, stabilise joints, reduce disability, and enhance the quality of life<sup>48</sup>. Once thought to be impossible, total symptom control and joint preservation are now attainable. It appears that fewer RA patients are having operations by orthopaedic

surgeons<sup>49</sup>. Surgery options include arthroscopy for diagnostic, preventive, or therapeutic purposes, synovectomy for therapeutic resection, arthrodesis, or total joint replacement (JTR). Surgery is typically performed to relieve pain and improve function. When other options have failed, surgery is performed. Patients with RA who underwent orthopaedic surgeries, including JTRS, saw a considerable improvement in their function and quality of life<sup>50</sup>. The most common surgeries involving major joints in RA patients are total hip and knee replacements (THR, TKR). Due to the population's ageing, there has been a significant increase in the number of these operations performed since the 1980s<sup>51</sup>.

### **Tenosynovectomy and synovectomy**

One of the earliest signs of rheumatoid arthritis is proliferative synovium and tenosynovium. Increased levels of collagenases, cytokines, and tenosynovium are found in diseased synovium and metalloproteinases that affect ligament and joint pain tears in a tendon<sup>52,53</sup>. Joint synovectomy and tenosynovectomy of the tendon are most suited for people who have early mild disease, substantially intact joint mobility, and swelling<sup>50</sup>. After a synovectomy, pain alleviation is often predictable, which touches on sensory denervation. Inferences have been made that tenosynovectomy can stop a tendon rupture from happening<sup>54</sup>. Early joint synovectomy may keep ligament and articular cartilage in good working order. Sadly, a single wrist synovectomy and no correlation exists between tenosynovectomy and disease remission, and there is currently no conclusive evidence that it causes long-term joint damage preservation; However, studies have shown that repeated major joint synovectomy can lower inflammatory mediator levels throughout the body<sup>55,56</sup>.

### **Arthrodesis**

Because technique produces a stable joint free from pain and inflammation, primary arthrodesis has a long history of usage in the treatment of rheumatic joints. As a result of patients' positive experiences with arthroplasties, the frequency has decreased during the past 20 years. However, there are still a few common reasons to do an arthrodesis. One is the foot, and the other is the cervical spine<sup>57</sup>. Getting a well-aligned, stable weight-bearing foot is the goal of treating the rheumatic foot. Newer treatments involve preventing metatarsal heads, for example via an oblique shortening osteotomy. To achieve this, arthrodesis of the first ray in combination with hammer-toe correction and excision of the metatarsal heads seem to be an effective procedure. In addition to the hand, the joint is where arthritis first appears. Different arthrodesis techniques can be used alone or in combination, depending on the affected joint a triple-arthrodesis, a navicular or subtalar arthrodesis, or a combination of the two (talonavicular, subtalar and calcaneo-cuboidal). Depending on the quality, stability, and nearby joints, arthrodesis or arthroplasty may be the best option for the ankle joint. There are several advantages to ankle arthroplasty over arthrodesis, including a range of motion that makes it easier to walk and lessens stress on the nearby proximal and distal joints<sup>58-60</sup>.

## **Resection-arthroplasty**

Inflammation weakens the soft tissue support structures around joints, which leads to instability and luxation. This may pose a constraint for resection arthroplasty procedures, which have diminished in importance as a result of the successful use of joint replacement. To stabilise the resected joint during interposition and restore function, some soft tissue is required<sup>61,62</sup>. Resection of the trapezium with or without interposition for the carpometacarpal joint is a well-established procedure; alternatively, arthroplasties and arthrodesis are used to treat a 90-90 malformation in the thumb joints<sup>60</sup>.

## **Radiosynoviorthesis (RSO)**

For the treatment of arthritic joint diseases of diverse origin in medium-sized joints such as the shoulder, elbow, wrist, hip, and ankle, RSO provides a local, comparatively non-invasive therapeutic technique. RSO can therefore oftentimes enable the patient to resume leading a relatively regular life. It is a technique for radioisotopically destroying the enlarged synovial tissue in its natural environment. The objective is to administer a chemical that kills sick tissue and, ideally, enables synovial membrane repair (synoviorthesis). The superficial synovial cells phagocytose the radiopharmaceutical. The discomfort and effusion are reduced as a result of the radiation's ability to stop the proliferative and destructive aspects of inflammation. Today, this type of therapy is regarded as a suitable second-line treatment for individuals who have not responded to other systemic or topical medications<sup>63</sup>.

## **Joint replacement therapy**

For most joints, also-arthroplasty has become the gold standard during arthritis. Rheumatoid arthritis indication is significantly more in juvenile arthritis than in osteoarthritis too.<sup>64,65</sup> Current advancements in technique and design have. Rising survival rates over time have made all-arthroplasty more common in arthritis than a standard operation. Due to the younger age of the patients who require revision operations this group of patients. A reliable plan must be developed. Because even one patient's multiple joints can be affected extremities. Hip and knee replacements are frequently required on the equal side<sup>66</sup>. Because one hand may be operated on, arthroplasty and arthrodesis became common treatments for wrist arthritis. For mobility and the other with arthroplasty for grip strength. For the proximal interphalangeal and metacarpophalangeal joint replacement surgery is still the gold standard because uncertainty implants that are not restrained run the danger of failing<sup>67</sup>.

## **Current issues in the management of RA**

Numerous significant questions have been raised as a result of the fast-growing number of biological choices for the treatment of RA patients. The first query relates to the best placement of the drugs within the therapy algorithm. Low disease activity or remission should be the goal of treatment, according to the 2012 update of the 2008 ACR recommendations for the use of biologic medicines and disease-modifying antirheumatic medications in the treatment of rheumatoid arthritis<sup>69</sup>.

## Conclusion

Inflammation and swelling of the synovium of the joint are symptoms of the widespread inflammatory disease RA, which is also known as rheumatoid arthritis (RA). If ignored, RA frequently leads to the loss of the joint's bony and cartilaginous components, as well as disability. The elevated mortality rate observed in RA patients relative to the general population is caused by a range of comorbidities linked to systemic inflammation. The physical examination, which reveals synovitis in numerous joints, and the patient's medical background are utilised to determine whether the patient has RA. This investigation's main goal is to improve RA management developed to guide treat-to-target pharmaceutical intervention techniques. Therefore updated treatment has been introduced but the knowledge about stem cell therapy is unaware so more updated information is needed.

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## Conflict of Interest

The article entitled Revolutionary Treatment of Rheumatoid Arthritis is herewith submitted for publication in Research Journal of Pharmacy and Technology. It has not been published before, and it is not under consideration for publication in any other journal. We certify that we have obtained written permission for the use of text, tables, and/or illustrations from any copyrighted source(s), and we declare no conflict of interest.

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