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Review Article

Rheumatoid Arthritis-Novel treatments

Rheumatoid Arthritis: Current and Emerging Paradigms of Diagnosis and Treatment

Rajni Kaur[1] and Hitesh Kumar Dewangan*

[1]*Department of Pharmaceutics, University Institute of Pharma Sciences (UIPS), Chandigarh University, Gharuan, Mohali, Punjab- 140413, India.*

[*]*University Institute of Pharma Sciences (UIPS), Chandigarh University, NH- 5, Ludhiana Mohali Highway, Mohali Chandigarh, Punjab (India)*

Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by inflammation and damage to joints and tissues. While previous reviews exist, there still needs to be more in understanding risk factors, diagnostic methods, and treatment options. This review aims to fill these gaps by providing a comprehensive overview of recent advancements in the field. To address the limitations of previous reviews, this article incorporates updated information on risk factors, including the influence of environmental factors in industrialized nations. It highlights the significance of early RA diagnosis and emphasizes the utility of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for effective disease management. Moreover, this review introduces innovative nanotechnology-based treatment approaches for RA. It explores the potential of gold nanoparticles, carbon nanotubes, polymer-based nanomedicine, and nanoliposomes in targeting specific inflammatory sites and improving treatment effectiveness. This review aims to present an up-to-date and comprehensive analysis of RA, bridging gaps in previous literature by introducing novel diagnostic techniques and exploring emerging treatment modalities. By synthesizing current knowledge and outlining future research prospects, this review aims to advance the understanding and treatment of rheumatoid arthritis. Additionally, this review discusses the systemic complications associated with RA, such as rheumatoid vasculitis and Felty syndrome. It also sheds light on the long-term consequences of untreated RA, including the potential need for joint replacement surgery (arthroplasty) and splenectomy. By providing a comprehensive analysis of these aspects, this review aims to enhance the holistic understanding of RA and guide future research toward improved management and patient outcomes.

Keywords: Rheumatoid arthritis (RA); Environmental factors; Genetic factors; DCE-MRI; NSAIDS; and Nanotechnology.

***Corresponding Author**

Hitesh Kumar Dewangan , University Institute of Pharma Sciences (UIPS), Chandigarh University, NH- 5, Ludhiana Mohali Highway, Mohali Chandigarh, Punjab (India)

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1. INTRODUCTION

Rheumatoid arthritis, a long-term autoimmune disorder, is thought to occur due to abnormal cellular interactions and impaired regulation of innate and acquired immune responses [1]. Indicators of rheumatoid arthritis are synovial hyperplasia, infiltration of lymphocytes, and aberrant synoviocyte proliferation, which finally result in erosive joint destruction [2]. Globally, there are different levels of RA prevalence, with industrialized nations often having a higher incidence due to environmental risk factors [3]. RA affects all age groups; the maximum affects the older person above 60. Approximately 1% of the global population has been afflicted by rheumatoid arthritis, and its ratio in males to females is 2.5:1 [4]. Compared to the wider population, those with rheumatoid arthritis have a 1.5 times higher probability of developing cardiovascular diseases [5]. Numerous research has found that the biggest causative factor for CV illness in RA patients is hypertension (HTN) [6]. The pathogenic process of RA is relatively unique, even though its genesis is still up for debate [7]. Pain, fatigue, and physical impairment are the most noticeable RA symptoms, which limit activity and worsen the quality of life [8]. Numerous inherited, genetic, environmental, and lifestyle factors have been identified as etiological factors for rheumatoid arthritis [9]. Standard criteria are frequently used to diagnose RA; defined recommendations are typically followed to treat this condition [10]. The use of imaging techniques in joint examination has increased dramatically with the advancement of quick imaging technology, including color Doppler ultrasound, X-ray photography, CT, magnetic resonance imaging (MRI), radionuclide imaging, and others. Drugs classified as non-steroidal anti-inflammatory medications (NSAIDs) are commonly employed to manage inflammation, ache, and fevers in animals and humans. Clinical trials conducted on a large scale have confirmed the efficacy of this medication in managing joint pain associated with osteoarthritis and rheumatoid arthritis in adults and adolescents [11].

2. NOMENCLATURE

Various terms are commonly employed to describe the phase of rheumatoid arthritis (RA) development that occurs before the manifestation of clinically detectable inflammatory arthritis (IA). These terms include Pre-RA, preclinical RA, and individuals deemed "at-risk." A study group associated with the European League Against Rheumatism (EULAR) coined Pre-RA in 2014 to characterize this specific stage [12]. Nonetheless, the term "Pre-RA" has certain limitations that must be considered. The EULAR study group specifically recommended its usage when individuals ultimately progress to the stage of clinically apparent rheumatoid arthritis (RA). An ongoing challenge is determining how to accurately apply this term to individuals who exhibit clinically evident inflammatory arthritis (IA) but fail to meet the established classification criteria for RA. In practical terms, such individuals are often managed clinically as if they have RA.

3. CURRENT MANAGEMENT OF PRE-RA

Individuals with symptoms and positive autoantibodies in the pre-RA stage are often considered for treatment initiation, even without clinically apparent IA. However, as not all individuals progress to IA, conducting trials becomes crucial in determining optimal interventions and duration. Referring eligible individuals to clinical trials is recommended. Still, if not feasible, risk reduction strategies include tobacco cessation, regular exercise, maintaining a healthy weight, and adopting a Mediterranean-style diet for broader health benefits, including cardiovascular health [13,14]. Insufficient data warrant refraining from supplement recommendations. Nevertheless, multiple studies suggest a potential inverse association between omega-3 levels, supplement intake, and the risk of autoantibodies and IA progression, necessitating further research [15]. Although periodontal disease has been identified in individuals in the pre-RA stage, and higher levels of perceived stress have been associated with developing IA/RA, more research is needed before recommending stress reduction and dental care as preventive interventions. It is crucial to emphasize that individuals at risk of IA/RA should promptly seek medical attention if they experience worsening joint symptoms. Regular follow-up, such as annual visits to a rheumatologist, can help assess joint health, offer ongoing counseling, and monitor for any changes [16, 17].

4. PREVENTION: RATIONALE, DESIGN, AND EXISTING STUDIES

Rheumatologists commonly focus on preventing further joint damage, osteoporotic fractures, and future flares in patients with established RA or acute gouty arthritis. However, preventing the initial manifestation of a disease is a relatively new concept. Clinical trials aiming to prevent clinically-apparent IA/RA have emerged due to factors like autoantibodies' predictive capacity, notably ACPA, and enhanced identification of individuals with biomarker elevations through clinical care. Screening high-risk populations, such as first-degree relatives of RA patients, is also employed [18-21]. Antimalarials have shown potential in preventing future flares in palindromic rheumatism [22]. Additionally, the "window of opportunity" concept in RA suggests that early treatment of established IA can lead to better outcomes and increased chances of drug-free remission, indicating the immune system's potential for normalization when treated promptly [23]. Two clinical trials have been conducted to prevent the initial manifestation of clinically-apparent IA. In one trial, 83 individuals with arthralgia, positive for ACPA and RF but without IA during physical examination, were randomly assigned to receive two doses of intramuscular dexamethasone (100 mg) with a six-week interval or placebo [24]. In the first trial, despite a decrease in autoantibody levels, there was no significant difference in IA rates between the dexamethasone-treated group (20%) and the placebo group (21%). In the PRAIRIE trial, where rituximab and methylprednisolone were administered, although the rates of IA were similar (34% treated vs. 40% placebo), the onset of IA was delayed by approximately 12 months in the treated group compared to placebo [25]. Several ongoing prevention studies include StopRA, which randomizes individuals with elevated ACPA levels to receive hydroxychloroquine or a placebo for 1 year, followed by a 2-year follow-up [26]. APPIPRA is randomizing individuals with high ACPA levels or ACPA plus RF and joint symptoms to receive abatacept or placebo for 1 year, with an additional 1-year follow-up [27]. Other studies involve statins in autoantibody-positive subjects and glucocorticoids/methotrexate in individuals with arthralgia and subclinical IA on MRI [28, 29].

5. RHEUMATOID ARTHRITIS SYMPTOMS

The symptoms of rheumatoid arthritis may vary among individuals but typically involve joint pain, swelling, and stiffness that tends to worsen in the morning or after extended periods

of inactivity. Although rheumatoid arthritis can affect any joint throughout the body, it frequently targets the hands, feet, and wrists, as shown in Figure 1. In some cases, RA can also cause systemic complications, such as inflammation of the lungs or blood vessels.

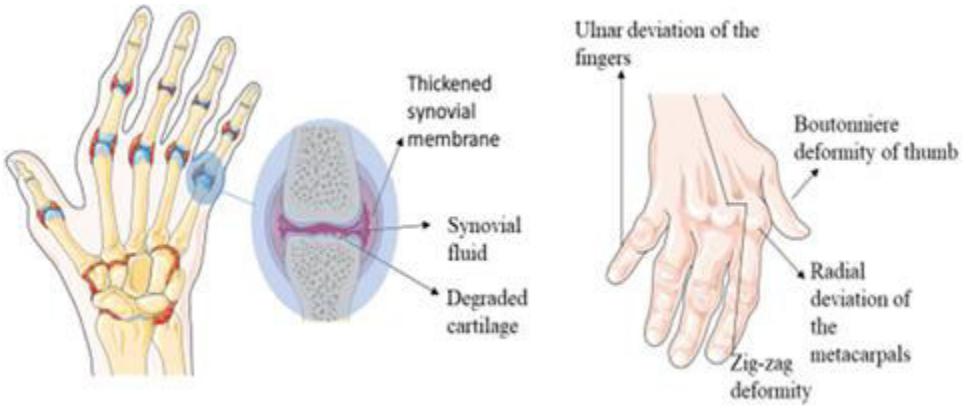


Fig 1: Symptoms of Rheumatoid arthritis [30].

Figure 1 Shows the autoimmune reaction, marked by the immune system's assault on the joints, leading to inflammation and subsequent damage to the joints, which is thought to be the root cause of rheumatoid arthritis. This autoimmune response results in the formation of antibodies, Examples of such are antibodies like rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), which contribute to inflammation development. Inflammation causes joint stiffness, edema, and ache, which can lead to joint damage over time if left untreated.

6. OVERVIEW OF RHEUMATOID ARTHRITIS (RA) PATHOGENESIS

The autoimmune disease called rheumatoid arthritis (RA) causes inflammation, synovial hyperplasia, and joint damage due to the body's defense system assailing healthy joint tissues. It affects multiple joints, causing aches, stiffness, and reduced mobility. Managing RA is an ongoing process to alleviate symptoms and prevent further joint damage. The pathogenesis of rheumatoid arthritis (RA) is an intricate process, including genetic, environmental, and immunological factors. These factors interact in a complex manner to activate immune cells and stimulate the generation of cytokines that promotes inflammation, eventually leading to the progression of rheumatoid arthritis (RA) [31]. New research has clarified the pathogenesis of RA, revealing that the stimulation of the innate immune response- namely macrophages and dendritic cells - is a crucial mechanism underlying the disease. The development of rheumatoid arthritis is linked to the production of multiple pro-inflammatory cytokines by immune cells, including TNF-α, IL-1, and IL-6. These cytokines have a substantial impact on the progression of the disease. The generation of pro-inflammatory cytokines stimulates the activation of T and B cells, producing autoantibodies such as RF and ACPA. The emergence of rheumatoid arthritis is often linked to the existence of these autoantibodies. These autoantibodies target and attack the synovial membrane, thereby playing a role in the advancement of rheumatoid arthritis (RA) [32]. Newer research has indicated that immune cells aside from macrophage and dendritic cells, for example, natural killer cells, mast cells, and regulatory T cells, could also have substantial involvement in the development of rheumatoid arthritis (RA). These cells contribute to the disease's pathogenesis alongside the previously studied immune cells, highlighting the complexity of RA's immune-mediated mechanisms. For example, mast cells are activated in the synovium and release histamine, prostaglandins, and leukotrienes, which amplify the inflammatory response. In contrast, natural killer cells promote synovial fibrosis and bone destruction by producing RANKL and MMPs. It suggests that the pathogenesis of rheumatoid arthritis (RA) involves the contribution of natural killer cells by producing these factors that promote joint damage [33]. The onset and advancement of rheumatoid arthritis (RA) may also involve the disruption of the gut microbiome and mucosal immune system regulation. Studies have shown a potential link between this disruption and the development of RA, further emphasizing the complex interplay of various factors in the disease's pathogenesis. Recent studies have highlighted modifications to the gut microbiota's composition and function and a compromised intestinal barrier function that may cause bacterial products and antigens to enter the bloodstream. This, in turn, activates the immune system and generates cytokines that promote inflammation, contributing to the progression of rheumatoid arthritis (RA) [34]. RA's pathogenesis has also been illuminated by genetic research. Genome-wide association studies (GWAS) have identified over 100 genetic loci linked to RA, a significant proportion of which are implicated in immune regulation and signaling pathways. These findings suggest that genetic factors are crucial in RA's development and highlight the importance of further genetic research in understanding the disease's pathogenesis. These genetic variants contribute to the susceptibility to RA by altering immune cell function and cytokine production. In summary, the pathogenesis of RA is a complex and multifaceted process involving intricate interactions between genetic, environmental, and immunological factors. More extensive research is necessary to comprehensively comprehend the disease's initiation and progression and develop innovative and efficient therapies for this incapacitating disorder [35].

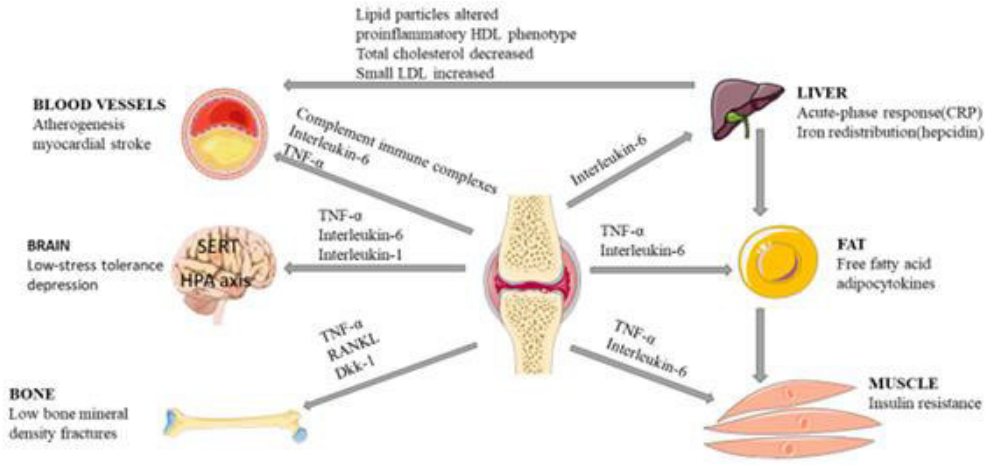


Fig 2. Depicted Rheumatoid arthritis pathogenesis [36].

While the exact pathogenesis of RA remains unclear, some researchers have identified the presence of ACPAs and rheumatoid factors in the serum of individuals with RA. Antibody synthesis causes inflammation, followed by the emergence of disease-related clinical symptoms. Citrullination, which is the arginine to citrulline conversion, results in an immunological reaction that suggests the development of ACPAs. Some common risk factors trigger the pathogenesis of rheumatoid arthritis.

7. RISK FACTORS OF RHEUMATOID ARTHRITIS

7.1. Genetic factors

Petrelli et al. mentioned in their review article the genetic aspects which cause rheumatic arthritis. Several genetic variants in Table 1, in class 1 (e.g., Human Leukocyte Antigen-A, B, C), class 2 (e.g., Human Leukocyte Antigen-DR, DP, DQ), and class 3 subregions of the MHC (major histocompatibility complex) genes have been linked to RA susceptibility [37]. Vetchinkina et al. indicated a strong relationship between the development of RA and the alleles HLA-DRB1*01, HLA-DRB1*04, HLA-B*27, TNF (rs1800629), PTPN22 (rs2476601), IL4 (rs2243250), and TPMT (rs2842934) as well as genotypes HLA-DRB*01:16, HLA-DRB1*04:04 [38]. On the background of HLA-DRB1*04:01, the formation of rheumatoid nodules may be influenced by immune complexes comprising anti-501-515cit antibodies and rheumatoid factors [39]. According to Requeiro et al., the MHC locus HLA-B*08 containing Asp-9 is strongly connected with anti-Carp+/CCP RA [40]. Cai et al. discovered a novel CircRNA (circular RNA). Circ 0088194 was found to be higher in RA-FLSs and associated with the disease activity score in 28 joints [41]. Zhi et al. revealed that the miR-375/TAB axis was the mechanism through which AFF2 triggered the Proliferation of FLS-RA cells and the subsequent inflammatory response. The measurement of circulating AFF2 may serve as a biomarker for diagnosing and managing rheumatoid arthritis [42].

Table 1. Pathogenesis of RA is influenced by genetic factors.

Serial no.	Genetic characteristics	Function	Ref.
1	HLA-B*08	Positivity for anti-carbamylated protein antibodies	38
2	HLA-DRB1*04	Susceptibility	38
3	HLA-DRB*04:01	Detection of anti-A501 citrullinated protein antibodies.	39
4	HLA-DRB1*01	Susceptibility	40
5	Circ_0088194	The miR-766-3p/MMP2 axis promotes RA-FLS invasion and migration.	41
6	Circ-AFF2	Rheumatoid arthritis synovial fibroblasts are stimulated to proliferate, respond inflammatoryally, migrate, and invade via the Circ-AFF2/miR-650/CNP axis.	42
7	circMAPK9	Susceptibility	43
8	lncRNA FOXD2-AS1	Promote the proliferation and invasive behavior of fibroblast-like synoviocytes in RA.	44
9	lncRNA SNHG14	LncRNA SNHG14 regulates the expression of proinflammatory cytokines in RA by modulating the miR 17-5p/MINK11-JNK pathway, leading to an increase in RA-associated inflammation.	45
10	lncRNA NEAT1	MiR-204 interacts with the promoter of miR-129 and induces its methylation.	46
11	linc00152	LINC00152 promotes RA FLS cell proliferation.	47
12	lincRNAS56464.1	Susceptibility	48
13	CD40	Inflammation and autoantibody synthesis are encouraged by the CD40/CD40L costimulatory pathway, which contributes to pathogenic processes.	49
14	CD209-96A variant	Susceptibility	50
15	MiRNA-22	Disease activity	51
16	IL-6	In the pathogenesis of RA, the pleiotropic cytokine interleukin 6 plays a crucial role (RA). In other words, individuals with rheumatoid arthritis exhibit elevated levels of	52

		it their synovial fluid and blood, and the level is correlated with the severity of their illness and joint damage.	
17	IRAK1(rs1059703)	Susceptibility and disease severity	[53]
18	IL-1R1	The IL1R1 gene, which codes for cytokine receptors, contributes to RA's tissue damage and inflammation.	[54]
19	IL-35	restricting FLS growth, angiogenesis, and bone resorption.	[55]
20	IL-21	Susceptibility and disease activity	[56]

Controlling the miR-140-3p/PPM1A through circMAPK9 knockdown may inhibit cellular growth, infiltration, movement, and inflammatory reaction while promoting apoptosis in RA-FLSs. This novel finding offers an improved comprehension of the underlying mechanisms implicated in the development of rheumatoid arthritis and suggests a potential therapeutic application of circMAPK9 inhibition [43]. Zhao et al. investigated the regulation of long non-coding-RNA (FOXD2-AS1) in the genesis of RA. They found in RA patients, synovial tissue, and serum samples, FOXD2-AS1 expression was increased [44]. According to reports, long noncoding RNAs (lncRNA) Function as competing endogenous RNAs and contribute to the pathogenesis of RA. Small nucleolar RNA host gene 14 (SNHG14), a lncRNA, has a role in the emergence of numerous illnesses [45]. A prospective diagnostic and therapeutic biomarker for RA, lncRNA NEAT1, has been shown to encourage invasion and migration in RA-FLSs. Xiao et al. focused on the mechanism behind the function of the lncRNA NEAT1 in RA [46]. Zhang et al. discovered that the linc00152 expression requires the NF-kB signaling pathway, which is up-regulated in RA-FLS and promoted by TNF-α/IL-1 in a time and dose-dependent manner [47]. The long non-coding RNA LOC100912373 was revealed as a crucial gene related to rheumatoid arthritis to govern the PDK1/AKT axis [48]. SLE and RA are brought on and progress because of CD40's involvement in the inflammatory reaction and promotion of fibroblast growth [49]. Chann et al. reported that in rheumatoid arthritis patients, there is a positive correlation between elevated CD209 expression in immune cells and the severity of cartilage damage, and SNPs (single nucleotide polymorphisms) in the CD209 (cluster of differentiation 209) promoter region can potentially impact the level of expression (RA) [50]. Ciesla et al. have demonstrated in this research for the first instance that plasma levels of microRNA-22 might function as probable molecular markers of disease activity. Endogenous micro-RNAs (miRNAs), which are long, about 18-25 nucleotide, non-coding single-stranded RNAs, have been suggested as potential extracellular biomarkers of several disorders. By preventing translation or causing mRNA destabilization, they mostly reduce gene expression [51]. Hussain et al. found IL-6 (interleukin-6) and vitamin D receptor (VDR) changes in RA patients. They demonstrated the important role of vitamin D receptors and IL-6 gene polymorphisms in the genesis of rheumatoid arthritis [52]. Hosseini et al. found that the RA onset age in Iranian patients is influenced by the IRAK1 gene's rs1059703T allele (risk allele), which raises the chances of developing rheumatoid arthritis and the severity of the illness [53]. Liu et al. discovered that the Chinese Han population is more susceptible to RA was linked to SNPs in IL1R1 (rs1049057, rs3917318, rs956730) and SNPs in IL1R2 (rs2072472, rs3218896, rs719250, rs3218977, rs4851527) [54]. Interleukin-35 (IL-35), a novel inflammatory cytokine expressed in different immune cells with dual functions, is the latest addition to the IL-12 group. According to Xie et al., the synthesis of Interleukin-35 is abnormal in patients with rheumatoid arthritis [55]. The presence of IL-21 greatly impacts the pathophysiology of RA, and the IL-21 rs2055979 polymorphism is associated with levels of IL-21 in plasma, enhancing the vulnerability to the onset of RA in the Chinese population. [56].

8. ENVIRONMENTAL, DIETARY, AND LIFESTYLE FACTORS

RA has been linked to numerous environmental, nutritional, and lifestyle variables (such as Occupational dust (silica), Ambient air pollution, Ambient temperature, Exposure to tobacco smoke, High content of sodium, red meat, and iron consumption, inadequate vitamin D intake, Female sex, Obesity, Smoking Alcohol consumption) [40-46]. Occupational inhalable agents may pose a key environmental contributor to the development of anti-citrullinated protein antibody-positive, particularly in the presence of both smoking and gene associated with RA susceptibility [40]. Ho et al. carried out a community-based cohort study in Taiwan to investigate the association between exposure to ambient air pollution and the incidence of RA. They combined and analyzed two residential area databases, the Taiwan Air Quality-Monitoring Database (TAQMD) and the Longitudinal Health Insurance Database (LHID), as part of their study. They computed the incident rate of RA 10000 people in a year faced each quarter of PM2.5 and PM10. According to their study, exposure to PM2.5 is linked to a higher chance of developing RA [41]. Zhao et al.'., the study suggested that a drop in temperature may increase the chance of RA. Patients who were female and between the ages of 41 and 65 were most susceptible to the effect of temperature drop [42]. Zhang et al. investigated the relationship between exposure to secondhand smoke and the likelihood of developing RA, finding that exposure to passive smoking, especially during childhood, could be a potential risk factor for developing RA [43]. Valencia et al. reviewed that a red meat diet and high sodium intake are thought to cause RA and aggravate inflammation [44]. Smoking, a lack of calcium, and a deficit in vitamin D are risk factors that impact the general population but may be more prevalent in RA [45]. Koller-Smith et al. found that maintaining a standard body weight can prevent the risk of rheumatoid arthritis, as obesity is also a risk factor for this condition [46].

9. A PROPOSED MODEL IMPLICATING MULTIPLE PATHOGENIC MECHANISMS IN RA

Intertwined Pathogenic Pathways: Unveiling the Complexity of Rheumatoid Arthritis. This proposed model illustrates the intricate interplay of various mechanisms contributing to the development and progression of RA, including immune dysregulation, chronic inflammation, synovial hyperplasia, and joint destruction. Understanding these interconnected pathways is vital for advancing targeted therapeutic strategies.

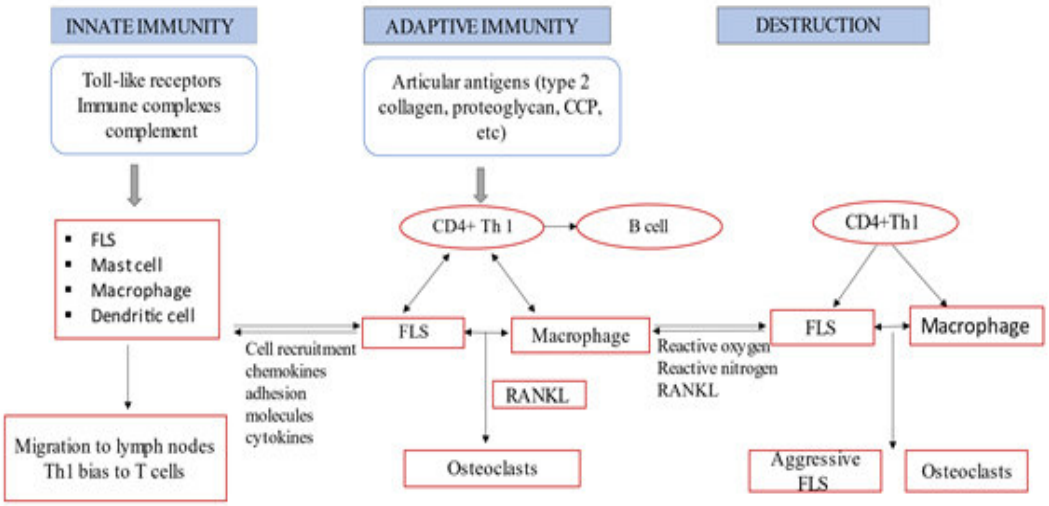


Fig 3: The proposed model of rheumatoid arthritis (RA) [57].

Figure 3 shows a step-wise progression involving innate immunity activation with cells like dendritic cells, macrophages, fibroblasts, and mast cells. It leads to the migration of immune cells into the synovium, triggering adaptive immune responses. Antigen presentation in the synovium influences T cells to adopt a TH1 phenotype. In the destructive phase, osteoclast activation driven by RANKL causes bone resorption, and synoviocytes can invade cartilage. These processes occur concurrently, with innate and adaptive immunity potentially activating in parallel, contributing to disease flares and remissions. Key components include dendritic cells (DC), cyclic citrullinated peptide (CCP), fibroblast-like synoviocytes (FLS), and macrophages (MØ).

10. EPIDEMIOLOGY AND CLINICAL FEATURES

Rheumatoid arthritis (RA) affects approximately 1% to 2% of the global population, equivalent to 60-120 million individuals worldwide. In the United States, it affects about 1% of the population. Women are three times more likely to be affected by RA than men. Although RA can occur at any age, it typically starts between 30 and 50. The disease's severity ranges from a self-limiting condition to a chronic and progressive ailment that leads to joint damage and deformity. Commonly experienced are extraarticular manifestations like malaise and fatigue. However, the prevalence of less frequent manifestations such as pleurisy, pericarditis, episcleritis, vasculitis, and rheumatoid nodules has decreased with more effective therapies. RA can reduce an individual's lifespan by 3 to 18 years [58]. In the United States, the average annual cost of medical care for an RA case is $5919 [59].

11. BIOLOGIC THERAPIES

Methotrexate, although beneficial in treating rheumatoid arthritis (RA), falls short of meeting all treatment needs. Up to 25% of patients on methotrexate do not experience improvement, and a significant portion still faces disease flares, requiring additional steroid treatment. Rheumatoid nodules may also enlarge or grow in about 15% of methotrexate-treated patients. However, advancements in understanding RA's molecular and cellular mechanisms have led to the development of innovative biologic therapies targeting specific cytokines and inflammatory pathways [60]. TNF-α inhibitors (etanercept, infliximab, adalimumab) and IL-1 inhibitor anakinra have effectively reduced disease activity. These breakthrough treatments, especially TNF-α blockers, have revolutionized RA management and provided hope for patients with limited response to traditional disease-modifying drugs [61].

12. MEASURING THE RESPONSE TO DRUGS IN RA

The primary outcome measure in RA clinical trials is the "ACR 20," which signifies a 20% or greater reduction in the number of tender and swollen joints, along with improvements in at least three out of five additional criteria, including assessments of pain, physical function, and markers of inflammation. Secondary outcome measures, such as the ACR 50 and ACR 70, represent higher levels of improvement (50% or more and 70% or more, respectively) [62].

13. TNF-α INHIBITORS

TNF-α inhibitors, including infliximab, etanercept, and adalimumab, treat rheumatoid arthritis (RA) by binding to TNF-α and preventing its interaction with target cells [63, 64]. These drugs exhibit a more rapid onset of action than traditional disease-modifying antirheumatic drugs (DMARDs) and can be combined with methotrexate [65, 66]. Infliximab is administered intravenously, while etanercept and adalimumab are administered subcutaneously. Adalimumab can be escalated to a higher dose for the additional therapeutic benefit [66]. However, these TNF-α inhibitors carry potential adverse effects, including an increased risk of infections, tuberculosis, and the development of malignancies and neurological events[67,68]. Hypersensitivity reactions and immune/autoimmune responses, such as forming anti-infliximab antibodies, can also occur [69]. Concomitant use of methotrexate is recommended to reduce immune responses [70].

14. ANAKINRA (IL-1 BLOCKADE)

IL-1, predominantly produced by monocytes and macrophages, contributes to joint damage in rheumatoid arthritis (RA) by stimulating matrix metalloproteinase release [71,72]. Anakinra, a recombinant IL-1 receptor antagonist, is given subcutaneously at 100 mg/day, showing effects within 2-4 weeks. It surpasses placebo efficacy when used alone or with methotrexate [73-75]. Methotrexate plus anakinra significantly

improved ACR 20 and ACR 50 responses [76]. Anakinra's primary adverse event is an increased risk of bacterial infections. Concurrent use with TNF-α inhibitors is not recommended due to infection risks, and daily injections may impact patient preference [77]. Anakinra is typically considered after anti-TNF-α failure, offering modest symptom improvement and radiographic progression inhibition.

15. ON THE HORIZON

Despite successful current therapies, the need for improved options in rheumatoid arthritis (RA) persists. Around 15% of patients have inadequate responses to biologics, and approximately 30% discontinue treatment within a year. Promising therapies on the horizon include Abatacept, Rituximab, and MRA, offering hope for addressing RA's unmet needs.

16. CTLA4-IG (ABATACEPT)

T-cell activation requires TcR-MHC II binding and interaction with costimulatory molecules on antigen-presenting cells [78]. CTLA4Ig, a fusion protein comprising cytotoxic T lymphocytes –associated antigen 4 and human IgG1, blocks CD80 and CD86 on antigen-presenting cells, inhibiting CD28 engagement on T cells. It attenuates the early inflammatory cascade in RA. A 6-month study demonstrated significant improvement with a 10-mg/kg dose of CTLA4Ig, showing lower serious adverse events compared to a lower dose or placebo plus methotrexate [79]. Long-term data show that combining CTLA4Ig with methotrexate is safe and effective in active RA, improving signs, symptoms, and quality of life, highlighting its potential as a promising new therapy [80-83].

17. ANTI-CD20 MAB (RITUXIMAB)

In a small open-label trial, rituximab demonstrated significant and sustained improvement in five patients with refractory rheumatoid arthritis (RA) [84]. Rituximab, a genetically engineered anti-CD20 monoclonal antibody, selectively depletes B cells by targeting the CD20 antigen [85]. In a subsequent randomized control trial, rituximab combined with methotrexate or cyclophosphamide showed response rates comparable to anti-TNFα therapies [86, 87]. Adverse event rates were similar across treatment groups. Phase III trials are ongoing to evaluate further rituximab's efficacy, long-term safety, and impact on radiographic changes.

18. IL-6RMAB (MRA)

IL-6 is a pleiotropic cytokine involved in immune response, inflammation, hematopoiesis, and bone metabolism [88]. Elevated IL-6 levels correlate with RA disease activity and joint damage[89]. MRA is a humanized anti-IL-6 receptor antibody that blocks IL-6 binding to its receptor [90]. MRA is administered as 60-minute infusions every 4 weeks. A recent 3-month double-masked, placebo-controlled trial in 164 patients with active RA demonstrated MRA's safety profile and clinical benefits [91]. The results of the ongoing CHARISMA study, evaluating the MRA in 359 methotrexate partial/non-responders, are currently being analyzed and reviewed [92].

19. DIAGNOSIS OF RHEUMATOID ARTHRITIS

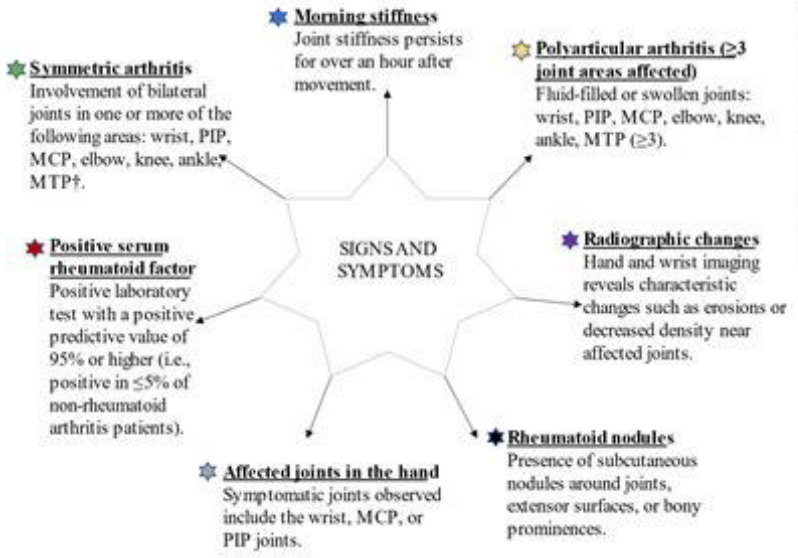
The process of diagnosing rheumatoid arthritis involves a comprehensive evaluation of clinical symptoms, along with the use of laboratory and imaging tests to support the diagnosis. The following points describe the diagnosis of RA, it includes:

20. TYPICAL PRESENTATION

Rheumatoid arthritis is diagnosed based on clinical observations. Patients usually have pain and stiffness in multiple joints, which can start gradually over weeks or months, with some cases having a faster onset triggered by specific events. The joints most frequently affected by rheumatoid arthritis are those with a higher proportion of synovium to articular cartilage. The wrists and the proximal interphalangeal and metacarpophalangeal joints are commonly involved. The distal interphalangeal joints and sacroiliac joints are typically spared from involvement [93]. Rheumatoid joints are typically soft, tender, and warm but not red. "Puffy" hands may be reported. Atrophy of nearby muscles, disproportionate weakness, and morning stiffness lasting ≥45 minutes are common. Flexed joint positions, low-grade fever, fatigue, and malaise can occur [94].

21. DIAGNOSTIC CRITERIA

The formal diagnosis of rheumatoid arthritis in clinical trials involves using seven criteria established by the American Rheumatism Association (ARA) (figure 1) [95, 96]. Diagnosing rheumatoid arthritis in outpatient settings, particularly in the early stages, can be difficult. During the initial visit, healthcare providers assess the patient's pain intensity, duration of stiffness and fatigue, and functional limitations. A thorough joint examination plays a vital role in the diagnostic process.



SIGN	LR +ve	LR -ve	% with rheumatoid arthritis if sign or symptom is*:
			Present Absent
★	1.9	0.5	39 14
★	1.2	0.6	29 17
★	8.4	0.4	74 13
★	11	0.8	79 21
★	3.0	0.98	50 25
★	1.5	0.4	33 12
★	1.4	0.5	32 13

*—Assumes an overall probability of rheumatoid arthritis of 30 percent.

†—PIP, MCP, and MTP joints need not be absolutely symmetrical.
LR+ = positive likelihood ratio;
LR-= negative likelihood ratio;
PIP=proximal interphalangeal;
MCP=metacarpophalangeal
MTP=metatarsophalangeal

Fig 4: Classification of rheumatoid arthritis according to Revised American Rheumatism Association Criteria [95,96].

This figure presents the diagnostic significance of various clinical features for rheumatoid arthritis (RA) based on positive likelihood ratio (LR+), negative likelihood ratio (LR-), and the percentage of individuals with RA when the sign or symptom is present or absent. The features include morning stiffness, arthritis of three or more joint areas, hand joint involvement, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor positivity, and radiographic changes. The values provided assume an overall probability of RA of 30 percent. These findings can aid clinicians in evaluating and diagnosing RA in patients.

22. DIFFERENTIAL DIAGNOSIS

Differentiating rheumatoid arthritis from other conditions is crucial. Similar symptoms can be seen in infection-related reactive arthropathies, seronegative spondyloarthropathies, systemic lupus erythematosus, and other connective tissue diseases [97,94]. Furthermore, certain endocrine and other disorders can mimic rheumatoid arthritis. Although gout rarely coexists with rheumatoid arthritis, joint aspiration should be considered if gout is suspected. Rheumatoid arthritis can mimic several other conditions, as mentioned below:

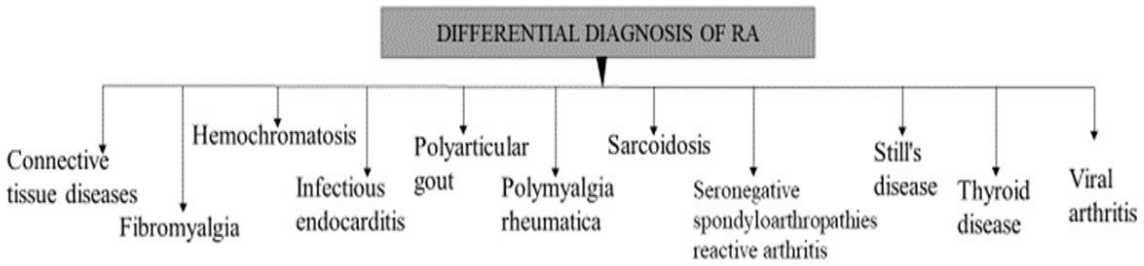


Fig 5: Differential diagnosis of RA [97].

Various conditions, including connective tissue diseases, fibromyalgia, hemochromatosis, infectious endocarditis, polyarticular gout, polymyalgia rheumatica, sarcoidosis, seronegative spondyloarthropathies/reactive arthritis, Still's a disease, thyroid disease, and viral arthritis, can present similar symptoms to rheumatoid arthritis. To differentiate between these diseases, specific evaluations are necessary. For example, fibromyalgia can be distinguished by tender trigger points, while hemochromatosis requires assessing iron studies and skin color changes. Infectious endocarditis with murmurs, fever, and a history of IV drug use should be considered. Polyarticular gout involves uric acid crystals and potential coexistence with calcium pyrophosphate deposition disease. Polymyalgia rheumatica primarily affects proximal joints, sarcoidosis involves hypercalcemia and abnormal chest X-ray findings, and seronegative spondyloarthropathies/reactive arthritis typically show asymmetrical joint involvement and associations with psoriasis or inflammatory bowel disease. Still's disease exhibits systemic symptoms, and thyroid disease is evaluated based on specific symptoms and thyroid-stimulating hormone levels. Viral arthritis, which mimics arthritis symptoms, should be considered in recent viral illness cases. Accurate diagnosis and effective management require a comprehensive evaluation by a healthcare professional.

23. DIAGNOSTIC TESTS

Various tests aid in diagnosing and monitoring rheumatoid arthritis, but no single test can definitively confirm it. The American College of Rheumatology recommends baseline

laboratory evaluations, including a complete blood cell count with differential, rheumatoid factor, and measurements of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). These tests provide objective data that assist in accurately assessing the condition. Assessing the baseline renal and hepatic function is also recommended, as it helps determine the appropriate medication options. Laboratory and imaging findings associated with rheumatoid arthritis include various tests that help diagnose and monitor the disease. Some of these findings include [72,93,97].

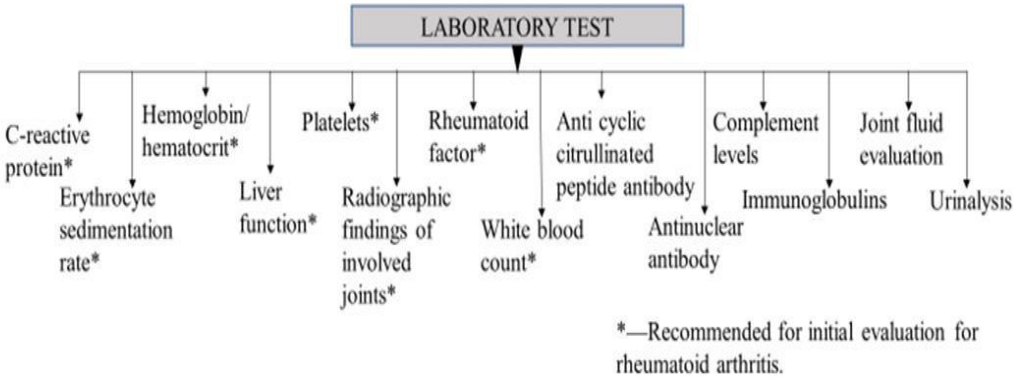


Fig 6: Laboratory tests [93,97].

Laboratory and imaging findings are crucial for diagnosing and monitoring rheumatoid arthritis (RA). C-reactive protein (CRP) is commonly measured and is typically elevated in RA, indicating inflammation. Monitoring CRP levels helps track disease progression. Erythrocyte sedimentation rate (ESR) is another marker of inflammation that is often increased in RA, serving as an indicator of disease activity. Hemoglobin and hematocrit levels are slightly decreased in RA, suggesting normochromic anemia. Liver function tests usually show normal or slightly elevated alkaline phosphatase levels. Platelet counts typically increase in RA individuals, reflecting the ongoing inflammatory process. Radiographic findings of affected joints may appear normal or show signs of decreased bone density (osteopenia) and erosions near joint spaces, particularly in the early stages of the disease. Wrist and ankle X-rays are commonly used for baseline comparisons in future assessments. Rheumatoid factor, a frequently measured antibody, may be negative in 30 percent of early RA cases and is not considered a reliable indicator of disease progression. White blood cell count may be increased, reflecting inflammation. The anti-cyclic citrullinated peptide antibody (anti-CCP) correlates well with disease progression and is more specific for RA compared to rheumatoid factor. However, its availability may vary among laboratories. Antinuclear antibody testing is unreliable for screening RA but may be evaluated in certain cases. Complement levels are typically normal or elevated in RA, and immunoglobulins, particularly alpha-1 and alpha-2 globulins, may also be elevated. Joint fluid evaluation can aid in uncertain diagnoses. In RA, the joint fluid appears straw-colored with fibrin dots, which is negative for crystals and culture. The white blood cell count is typically between 5,000 and 25,000 per mm3, predominantly consisting of polymorphonuclear leukocytes. Glucose levels in the fluid are usually low. Urinalysis may reveal microscopic hematuria or proteinuria, which can be present in various connective tissue diseases, including RA. These urinary findings contribute to the evaluation of the overall disease process. Various methods are used to diagnose rheumatoid arthritis. We highlighted some important methods which some researchers use are listed in Table 2. Lin et al. designed an electrochemical sensor utilizing peptides and electrochemical impedance spectroscopy to identify autoantibodies to diagnose RA. They first confirmed that the newly created peptide had high sensitivity and could be used with the anti-CCP ELISA, which is now the gold standard approach [98]. Using RNA modification, Zhao et al. discovered RA diagnostic indicators and investigated the significance of immune cell infiltration. The T-FH (T cells follicular helper) penetration was positively linked with CLP1, which has been proven a reliable RA diagnostic marker [99].

Table 2. The recent methodology used to treat Rheumatoid arthritis.

S. No.	Treatment methods	Examples	Ref
1	Nanoparticle-based drug delivery system	Dexamethasone loaded radially mesoporous Silica, BAC loaded mPEG- PLGA NPs	100
2	Peptide-based nanotherapeutics	Methotrexate	101
3	Surface-modified bilosomes nano gel	Alkaloid (berberine)	102
4	Tolmetin sodium fast-dissolving tablet	Tolmetin sodium	11
5	anti-TNF therapy	ATRPred tool	103
6	Combination therapy	HDAC, IMPDH, and mTOR inhibitors combined with a JAK inhibitor	104
7	ADSC	-	105
8	Daphnes cortex	Traditional Chinese herbal medicine	106
9	Silk fibroin hydrogel	Sesbania sesban L. extract	107
10	Exercise therapy and self-management	Care hand app	108
11	Injectable drug delivery system	Generic drugs and nanoparticles	109
12	Transdermal film	Methotrexate	110

13	Disease-modifying anti-rheumatic drugs	Trypterygium glycoside	[111]
14	Glucocorticoids	Steroid hormone	[112]
15	NSAIDS	Ibuprofen, Naproxen, diclofenac, Indomethacin, and Coxibs	[113]
16	Gold nanoparticle (Au Pa)	Methotrexate	[114]
17	Nanoconjugate of Gold and Resveratrol	Resveratrol	[115]
18	Nanotube coupled with Methotrexate	Methotrexate	[116]
19	Polymer based methotrexate	Nanomedicine	[117]
20	Dextran sulfate-based MMP-2 enzyme	Nanomicelles	[118]
21	Mixed monoclonal antibodies with high loading	Rituximab, Adalimumab, and Trastuzumab	[119]
22	β -glucan nanoparticles	Targeted drug delivery of methotrexate	[120]
23	Nanoliposomes based transdermal hydrogel	Targeted delivery of methotrexate	[121]
24	Crocin-loaded nanoliposomes	Crocin	[122]

Using thermography (Thermo JIS), a fast and non-intrusive imaging device of the hands, Morales-Ivorra et al. characterize a new computational approach based on machine learning to quantify inflammation joints in rheumatoid arthritis [123] automatically. A quick, non-invasive thermography imaging method creates a heat-related image that bodies radiate. Even in RA patients who were in clinical remission, Thermography identified inflammation in joints [124]. Rheumatoid joint X-ray examination is widely available, affordable, and has standardized methods for interpretation. It also has drawbacks, such as the incapacity to accurately predict structural change in less than 6 to 12 months [125]. Although important for diagnosing rheumatoid arthritis, modern imaging techniques such as X-rays, computed tomography, magnetic resonance imaging, and ultrasound are limited. A multiplanar view of the entire joint is possible with CT, which can also identify subtler bone changes. Ionizing radiation is present in CT, but it is still unresponsive to changes in soft tissues [126]. Huang et al. used the ultrasonography machine to detect RH in 30 joints (figure 1) [127]. To address the issue of using dynamic contrast-enhanced MRI for rheumatoid arthritis diagnosis, Zhang et al. gave an application study using dynamic contrast-enhanced MRI for rheumatoid arthritis staging diagnosis. Using DCE-MRI to assess rheumatoid arthritis patients' activities is highly valuable (RA) [128]. Diagnostic methods and many more available methods for treating rheumatoid arthritis as shown in Figure 7 [122].

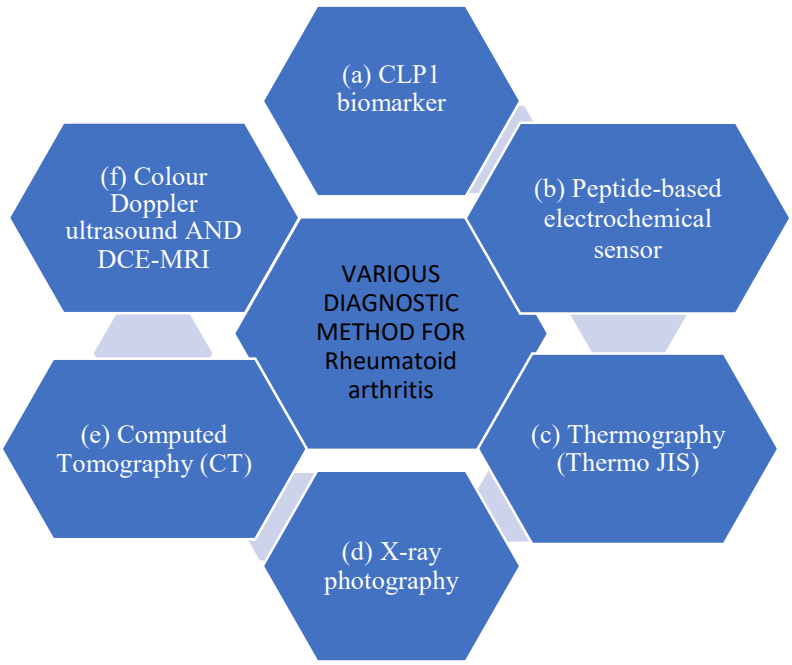


Fig 7: Illustrates Various diagnostic methods for Rheumatoid arthritis [129].

RA can be diagnosed using several diagnostic methods, including measuring the levels of CLP1 biomarkers in the blood, using a peptide-based electrochemical sensor to detect ACPA antibodies, thermography to measure joint temperature, taking X-ray photographs to detect joint damage, using CT scans to visualize joint deformity, and using ultrasound and DCE-MRI to detect inflammation. These tests are often used in conjunction with other clinical evaluations to make an accurate diagnosis of rheumatoid arthritis and start early therapy/management to prevent joint damage.

24. TREATMENT OF RHEUMATOID ARTHRITIS

Various recent methods used to treat Rheumatoid arthritis are listed in Table 2. Nasra et al. introduced a nanoparticle-based drug delivery method which is a priming method for enhancing drug delivery in addition to nanocarrier design. While targeted drugs have successfully treated RA, they have certain drawbacks, such as a less-than-ideal safety profile. Specifically, some targeted carriers may tend to distribute to unintended tissues, leading to potential toxicity [100]. For the

delivery of nanotherapeutics, peptides are frequently utilized as targeting moieties. In addition to regulatory considerations for peptides, a summary of numerous peptides with therapeutic applications in rheumatoid arthritis is provided [101]. Pathade et al. formulated Chitosan-coated bilosomes loaded with berberine are being used for the first time as a nano gel in treating RA inflammation [102]. A fast-dissolving tablet of tolmetin sodium was developed by Elsayed et al. for the diagnosis of RA. Tolmetin sodium is classified as a non-steroidal anti-inflammatory drug [11]. Prasad et al. invented an anti-TNF response predictor (ATRPred) machine, an ML-based classifier that can predict the anti-TNF therapy feedback in RA patients [103]. Numerous investigations have demonstrated that cytokines are crucial controllers of rheumatoid arthritis (RA). A change in the enzymes HDAC, IMPDH, mTOR pathway, and JAK pathway increases the number of cytokines in synovial inflammation. This elevated cytokine level is the cause of the inflammation in the treatment of RA; Mane et al. have concentrated on the developments of combining a mechanistic target of rapamycin inhibitor with a Janus kinase inhibitor and an HDAC inhibitor with an Inosine monophosphate dehydrogenase inhibitor [104]. The anti-inflammatory and neuroprotective properties of adipose tissue-derived mesenchymal stem cells make them potential therapeutic agents for rheumatoid arthritis [105]. Meng et al. introduced the Chinese traditional medicine named, Daphenes cortex, used for managing RA [106]. Pham et al. formulated a hydrogel made of silk fibroin which contains an extract of sesbania sesban L., and silk fibroin hydrogel has a strong anti-inflammatory activity that is used for managing RA [107]. Sanchez et al. recommended using the Care Hand smartphone app as a potentially helpful tool for rheumatoid arthritis self-management and exercise therapy [108]. Bruno et al. introduced an injectable drug delivery system for the management of RA. The parenteral system may consist of either generic drugs or nanoparticles [109]. Nornberg et al. formulated transdermal films, which consist of methotrexate drugs for managing RA [110]. The safety profile of the combination of Tripterygium glycoside (TG) is excellent, and it is more effective than traditional monotherapy of disease-modifying anti-rheumatic drugs in treating symptoms of rheumatoid arthritis [111]. Glucocorticoids, steroid hormones, are commonly prescribed to manage several autoimmune and inflammatory conditions, including rheumatoid arthritis [112]. NSAIDs are a type of medication that is the main form of treatment for RA patients who experience pain and stiffness [113]. Some nanotechnology-based drug delivery systems, such as Sphere gold nanoparticles, Rod gold nanoparticles, Carbon nanotubes, Polymeric nanoparticles, and Nanoliposomes, are used to manage RA [100]. Li et al. synthesized and formulated methotrexate-based nanogold particles to manage RA. They synthesized gold nanoparticles (AuNPs) at about 11-20 nm with the help of citrate reduction of acid chloroauric ($HAuCl_4$). A 5 ml aqueous solution containing 1 mM HAuCl4.3H2O was boiled and then combined with 10 ml of 1 wt% trisodium citrate Na3C6H5O7.2H2O solution and boiled again. The solution was continuously stirred and cooled at room temperature until it turned a deep red color. The mixture was subjected to high-speed centrifugation to eliminate any unbound citrate, and the resulting pellet was resuspended thrice in PBS with a pH of 7.4. A solution of MTX (1.5 mg/ml) and AuNPs were co-incubated in a 3:4 ratio at 37 °C for 48 hours to load the drug. Afterward, the mixture underwent centrifugation at 15,000 rpm for 20 minutes, and the resulting pellet was purified and then dissolved in PBS [114]. Nanotechnology was developed because of the specific physical and chemical characteristics of nanomaterials. Nanomaterials enhanced the bioavailability and targeted the damaged tissues in rheumatoid patients. Jaffer et al. developed a nanoconjugate of nanogold particles and resveratrol. The researchers performed the functionalization of resveratrol with gold nanoparticles AuNPs-PEG-Res) by swirling 15 ml of AuNPs while still warm. After introducing 2.175ml of 0.04mM aqueous PEG while stirring, the researchers added 3.425ml of aqueous Res dropwise into the mixture while stirring at 150rpm for 2 hours at 40°c to prepare Resveratrol-conjugated AuNPs-PEG (referred to as AuNPs-PEG-Res). The aqueous Res was prepared by dissolving 0.5mg of Res powder in 15 ml of D.W. During the preparation of AuNPs-PEG-Res, a warm solution of 15 mL of AuNPs was stirred, and 2.175 ml of 0.04 mM aqueous PEG was added. After that, 3.425 mL of aqueous Res was slowly added to the mixture dropwise, prepared by mixing 0.5 mg of Res powder in 15 mL of D.W. The stirring continued for 2 hours at 40°C, forming Red-conjugated AuNPs-PEG (AuNPs-PEG-Res) [115]. Kofoed Andersen et al. developed a nanotube with methotrexate for treating rheumatoid arthritis. They used HiPco and carboxyl carbon nanotubes, which act as a carrier for methotrexate (MTX) anti-inflammatory drugs. They used PEGylation to solubilize the nanotubes, which were then covalently loaded with MTX. The authors noted that SWCNTs exhibited selective accumulation in inflamed joints, as observed in a mouse serum transfer model. The authors also examined the performance of the MTX/siRNA-loaded nanotubes in the presence of human blood and mouse bone marrow cells. They discovered that carbon nanotubes possess the capacity to deliver therapeutic cargo to immune cells that are implicated in rheumatoid arthritis [116]. Marasini et al. developed a polymeric-based nanomedicine for the treatment of rheumatoid arthritis. They developed various hyper-branched polymers OEGMA-based with Methotrexate that has been and hasn't been alpha carboxylated coupled through a hexapeptide linker that is cleavable by MMP-13. The methotrexate-modified polymer has shown potential in vivo and in vitro behavior, indicating that it should be further developed and optimized as an anti-rheumatic nanomedicine [117]. Yu et al. prepared Cell- loaded DPC micelle using the dialysis method. They dissolved 10 mg of DPC in a liquid mixture (DMAP: DMF = 1: 0.8) in terms of DMAP and DMF and 1-milligram Cell in 1 ml DMAP. They stirred and mixed these proportions with a magnetic stirrer. Dialyze the combined solution in 24 hours of dialysis using deionized water (MWCO 3500 Da), changing the deionized water to 118 every two hours. He et al. synthesized tri-loaded monoclonal antibody nanoparticles and then they these antibodies into the surrounding of RA to produce high-loaded mixed antibodies of polymeric nanoparticles and used for managing RA[119]. Chen et al. formulated β- glucan nanoparticles linked with methotrexate for managing RA [120]. Zhao et al. used the thin film hydration method to develop DS-FLs/DEX. In brief, a combination of chloroform and methanol (6 mL, v/v = 1:3) was used to dissolve mild DOTAP, DOPE, CHOL, and DEX. The organic solvents were then evaporated for an hour at 40 °C to eliminate them. The thin film was dried by a vacuum drier for one hour and then stored at 4 °C overnight, and then it was hydrated for 2 hours in 5 mL of a phosphate buffer solution with mild DS solution with edge activators to obtain the DS-FLs/DEX. After that, they prepared DS-FLs/DEX-loaded hydrogel to manage RA as a transdermal drug delivery system [121]. Mohammadi et al. formulated crocin-loaded nanoliposomes for the treatment of RA [122].

25. FLOW DIAGRAM FROM THE TREATMENT APPROACH FOR A PATIENT WITH RHEUMATOID ARTHRITIS

The process of joint destruction in rheumatoid arthritis initiates shortly after symptoms appear, and initiating early treatment reduces the speed of disease progression [130]. It is crucial to diagnose rheumatoid arthritis and initiate treatment promptly. According to the ACRSRA, patients with suspected rheumatoid arthritis should be referred within three months for diagnosis confirmation and the start of treatment with disease-modifying antirheumatic drugs (DMARDs). The therapeutic objectives in rheumatoid arthritis encompass maintaining functional ability and quality of life, reducing pain and inflammation, safeguarding joints, and managing systemic complications [72, 93].

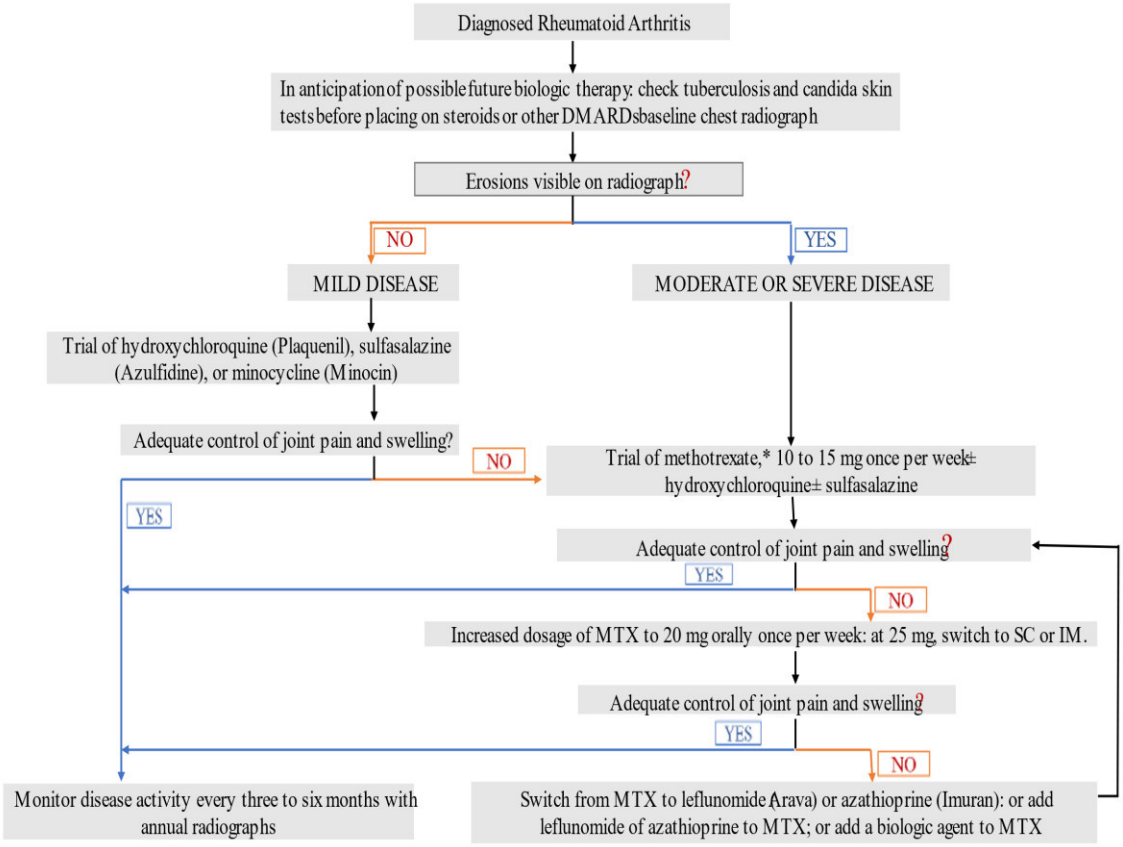


Fig 8: Flow diagram from the treatment approach for a patient with Rheumatoid Arthritis

26. SUMMARY OF MAIN IMMUNE-TARGETED THERAPIES FOR RHEUMATOID ARTHRITIS

The progress made in comprehending the pathogenesis of rheumatoid arthritis has been instrumental in paving the way for significant advancements in developing novel therapeutic agents. These agents are outlined in Table 3.

Table 3: Summary of main immune-targeted therapies for rheumatoid arthritis.

Therapy	Moa	Target Molecules	Example of Drug	Route	Side Effects	Onset of Action	Structure	Special Consideration	Ref
Tumor Necrosis Factor (TNF) Inhibitors	Block the action of TNF, a pro-inflammatory cytokine involved in RA pathogenesis	TNF-alpha	Adalimumab, Etanercept, Infliximab	SC, IV	Injection site reactions, infections	Weeks to months	Large protein-based biologics	Tuberculosis screening	131
Interleukin-6(IL-6) Inhibitors	Inhibit IL-6 signaling, reducing inflammation and joint damage	IL-6	Tocilizumab, Sarilumab	SC, IV	Elevated liver enzymes, infections	Days to weeks	Laboratory abnormalities in lipid profile	Monoclonal antibodies	132

Janus Kinase (JAK) Inhibitors	Target JAK enzymes involved in the signaling pathways of multiple pro-inflammatory cytokines	JAK 1, JAK 3, or JAK 1/2	Tofacitinib, Baricitinib	Oral	Infections, liver abnormalities	Weeks to months	Small molecule inhibitors	Increased risk of infections	[133]
T-cell Co-stimulation Blockers	Disrupt the co-stimulation process required for T-cell activation	CTLA-4	Abatacept	IV	Infections, infusion reactions	Weeks to months	Fusion protein	Increased risk of respiratory tract infections	[134]
B-cell Depleting Agents	Target B-cells involved in the production of autoantibodies	CD20	Rituximab	IV	Infusion reactions, infections	Weeks to months	Monoclonal antibodies	Increased risk of infections	[135]
Interleukin-1(IL-1) Inhibitors	Inhibit the activity of IL-1, a cytokine involved in the inflammatory cascade	IL-1 beta	Anakinra, Canakinumab	SC, IV	Injection site reactions, infections	Days to weeks	IL-1 receptor antagonist, Monoclonal antibody	Not recommended in active infections	[136]
T-cell-directed Therapies	Target-specific T-cell subsets involved in the pathogenesis of RA	IL-12/IL-23 or IL-17	Ustekinumab, Secukinumab	SC	Infections, injection site reactions	Weeks to months	Monoclonal antibodies	Increased risk of infections	[137]

Table 3: A diverse arsenal of targeted therapies for rheumatoid arthritis (RA) aims to tame the raging inflammation. Tumor Necrosis Factor (TNF) inhibitors like Adalimumab and Infliximab neutralize the pro-inflammatory cytokine TNF, while Interleukin-6 (IL-6) inhibitors such as Tocilizumab suppress IL-6 signaling. Janus Kinase (JAK) inhibitors like Tofacitinib target multiple cytokines' signaling pathways, and T-cell Co-stimulation blockers like Abatacept disrupt T-cell activation. B-cell-depleting agents, Interleukin-1 (IL-1) inhibitors, and T-cell-directed therapies provide additional strategies. However, careful monitoring and management of side effects are essential for optimal treatment outcomes.

27. DIAGRAMMATIC REPRESENTATION OF THERAPEUTICS TARGETS IN RA

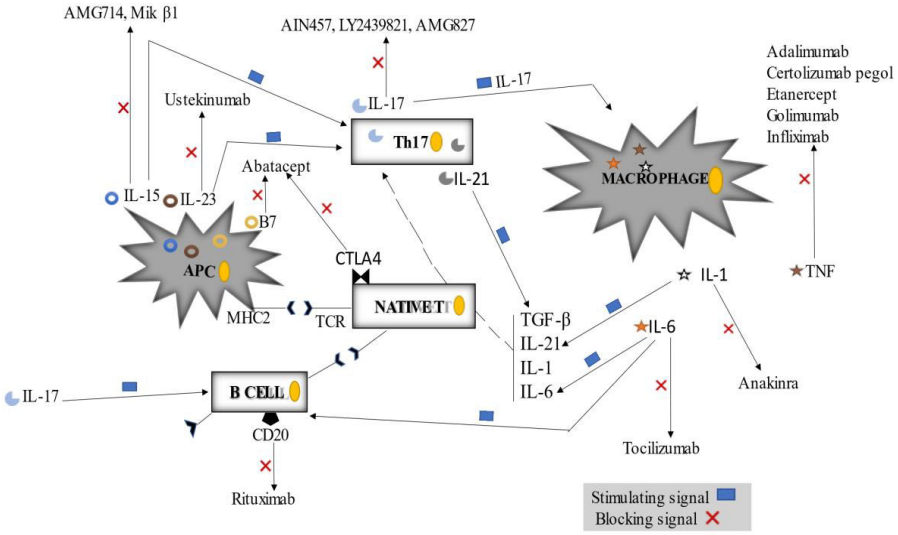


Fig 9: Diagrammatic representation of Therapeutic Targets in Rheumatoid Arthritis[138].

The cytokine profile is characterized by the involvement of T helper type 17 (Th17) cells. These cells produce the defining cytokine IL-17, which stimulates the production of IL-1, IL-6, and TNF from macrophages/monocytes. The differentiation of naive T cells into the Th17 phenotype is influenced by specific cytokines such as TGF-β, IL-1β, IL-6, IL-21, and IL-23, with IL-15 and IL-23 further reinforcing this phenotype. This article discusses therapeutic agents and their targets, highlighted in red, that aim to modulate these cellular pathways. These targets include antigen-presenting cells (APCs), interleukins (IL), major histocompatibility complex II (MHC II), matrix metalloproteinases (MMPs), T-cell receptors (TCRs), transforming growth factor (TGF), and tumor necrosis factor-α (TNF-α).

28. CURRENT PREDICTION MODELS FOR FUTURE RA

Multiple case-control studies consistently demonstrate that elevated serum levels of ACPA and RF have high positive predictive values (PPVs) for future IA/RA development, often exceeding 80% [139,140] (Table 4). Prospective studies incorporating ACPA (+/- RF), symptoms, and other factors report PPVs ranging from approximately 30% to over 70% for IA/RA development within 2-6 years. Individuals with high levels of autoantibodies or dual positivity for ACPA and RF tend to have the highest PPVs [144]. A Dutch study with 347 subjects with RF and ACPA positivity and joint symptoms but no IA at baseline found that 35% developed IA within a median of 12 months among those with a baseline high-risk score incorporating ACPA, RF, and other factors, up to 74% developed IA/RA within 3 years [143]. In a United Kingdom study of 100 ACPA-positive individuals with arthralgia, 50% developed IA/RA after a median of 7.9 months. Notably, among individuals with a baseline high-risk score encompassing examination findings, symptoms, genetic and autoantibody testing, and an abnormal power-doppler ultrasound finding, approximately 68% developed IA within 24 months [144]. These studies provide valuable insights into the likelihood and timing of IA/RA development, aiding in counseling individuals about their future risk, determining appropriate follow-up intervals, and guiding trial participation. Accurate estimates of incident IA/RA occurrences within specific timeframes are crucial for robust clinical trial design [142,143,144]. The role of C-reactive protein, an inflammatory marker, in improving prediction models for pre-RA must be more consistent. Similarly, the potential of abnormalities in cytokines/chemokines, in conjunction with autoantibodies, for prediction requires further validation [141,142].

Table 4: Key longitudinal studies of pre-rheumatoid arthritis

S.No	Study Design	Authors and Published Year	Study Population and Occurrence of Ia/Ra	Key Observations	Study Location	Ref
1.	Prospective cohort study	Gan et al 2017 (81)	Out of the 35 individuals with baseline IA identified during health-fair screenings and who tested positive for ACPA+ (CCP3), 14 of them developed incident IA/RA within	Higher age, shared epitope positivity, and lower blood levels of omega-3 fatty acids were found to be associated with the progression to IA/RA.	USA	144

			an average follow-up period of 2.6 years.			
2.	Prospective study of subjects with arthralgia	Burgers et al 2017 (80)	Out of the 178 subjects with arthralgia who met the EULAR criteria for Clinical Suspect Arthralgia (CSA) at baseline, 44 individuals (18%) developed incident IA/RA within a median timeframe of 16 weeks.	This study validated the EULAR definition of Clinical Suspect Arthralgia. The presence of three or more factors, including symptom duration <1 year, MCP joint involvement, morning stiffness ≥60 minutes, more severe morning symptoms, FDR with RA, and difficulty making a fist with MCP tenderness, had an 84% sensitivity and a 30% PPV for developing IA/RA within two years. When applied by non-rheumatologist practitioners, the PPV for IA was only around 3%.	The Netherlands and Sweden	145
3.	A prospective study examined ACPA+ (CCP2) individuals with arthralgia referred to rheumatology clinics.	Rakieh et al 2015 (33)	Out of 100 ACPA+ individuals, 50 developed incident IA/RA within a median duration of 7.9 months.	A scoring system was developed based on tender joints, morning stiffness, shared epitope presence, high RF and/or ACPA levels, and ultrasound power Doppler findings. Individuals with the highest scores (>=2) had an incidence rate of over 41% for IA/RA within 24 months. For scores of >=4, the incidence rate increased to 68% within 24 months.	United Kingdom	144
4.	Prospective study of unaffected FDRs of patients with RA	Ramos-Remus et al 2015 (15)	Out of 819 first-degree relatives (FDRs), 17 individuals (2.1%) developed incident IA/RA within a span of 5 years.	ACPA positivity, with or without RF positivity, had 58-64% PPV for RA development.	Mexico	146
5.	Prospective study of ACPA and/or RF-positive subjects	de Hair et al 2013 (79)	Out of 55 subjects, 15 (27%) developed incident IA within a median of 13 months.	Individuals who were non-smokers and had normal body weight exhibited the lowest rates of progression to IA/RA.	The Netherlands	147

Table 4: Insights from prospective studies shed light on the development of inflammatory arthritis (IA) and rheumatoid arthritis (RA). Gan et al. (2017) identified factors like age, shared epitope positivity, and lower omega-3 fatty acid levels associated with IA/RA progression. Burgers et al. (2017) validated the EULAR definition for identifying at-risk individuals, emphasizing specific clinical factors. Rakieh et al. (2015) developed a scoring system incorporating various parameters to predict IA/RA incidence. Ramos-Remus et al. (2015) highlighted ACPA positivity as a significant predictor in first-degree relatives. de Hair et al. (2013) found non-smokers with normal body weight exhibited lower IA/RA progression rates. Location: the USA, the Netherlands, Sweden, the United Kingdom, and Mexico.

29. COMPLICATIONS

Untreated rheumatoid arthritis (RA) can lead to various complications. Untreated rheumatoid arthritis (RA) can lead to various complications, as discussed. Anemia is a common occurrence, often associated with disease activity, and most patients have anemia of chronic disease. Cancer risks may be increased, particularly lymphomas and leukemias, potentially due to treatments. Cardiac complications include pericarditis, atrioventricular block (rare), and myocarditis. Cervical spine disease can cause instability, subluxations, and myelopathy. Eye problems such as episcleritis can occur. Fistula formation may result in cutaneous sinuses near affected joints. Infections are more likely due to RA treatment. Hand joint deformities are common, including ulnar deviation, boutonniere deformity, swan neck deformity, and thumb hyperextension. Other joint deformities, frozen shoulder, popliteal cysts, and carpal/tarsal tunnel syndromes can develop. Respiratory complications involve lung nodules, cricoarytenoid joint inflammation, pleuritis, and interstitial fibrosis. Rheumatoid nodules can be found on various body surfaces. Vasculitis can manifest as arthritis, peripheral neuropathy, cutaneous lesions, and coronary arteritis, with increased risk in males, high rheumatoid factor titers, steroid use, and multiple disease-

modifying antirheumatic drugs. Additionally, there is an association with an increased risk of myocardial infarction [93].

30. CONCLUSION

Rheumatoid arthritis is a musculoskeletal autoimmune disease that has caused severe disability in individuals and has a global impact on people's lives. As a result, effective RA treatment is crucial for decreasing patients' discomfort and enhancing the cure rate. Researchers have not yet proved the pathogenesis of rheumatoid arthritis, so treating RA is more challenging. If the diagnosis of RA occurs in the early stage, then several methods can be used to manage rheumatoid arthritis. Nanotechnology has been used to treat RA. Despite its immaturity, nanotechnology has the potential to revolutionize disease diagnosis, treatment, and research. Nanotechnology is the best method for the future aspect of the management of rheumatoid arthritis.

31. ACKNOWLEDGMENT

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32. AUTHORS CONTRIBUTION STATEMENT

Rajni Kaur contributed to creating the first version of the manuscripts and played a key role in designing the figures and tablets. Hitesh Kumar Dewangan played an important role in conceptualizing and designing the manuscript and contributing significantly to the editing process.

33. CONFLICT OF INTEREST

Conflict of interest declared none.

34. REFERENCES

1. Petrelli F, Mariani FM, Alunno A, Puxeddu I. Pathogenesis of rheumatoid arthritis: one year in review 2022. Clin Exp Rheumatol. 2022;40(3):475-82. doi: 10.55563/clinexprheumatol/l9lyen. PMID 35333708.
2. Chen X, Wang K, Lu T, Wang J, Zhou T, Tian J, et al. Qiao adiponectin is negatively associated with disease activity and Sharp score in treatment-native Han Chinese rheumatoid arthritis patients. Sci Rep. 2022;12(1):1. doi: 10.1038/s41598-022-10069-9.
3. Finckh A, Gilbert B, Hodkinson D, Lauper K. Global epidemiology of rheumatoid arthritis. Nat Rev Rheumatol. 2022;18(10):591-602. doi: 10.1038/s41584-022-00756-5.
4. Liang HY, Yin HX, Li SF, Chen Y, Zhao YJ, Hu W, et al. Calcium-Permeable Channels Cooperation for rheumatoid arthritis: therapeutic opportunities. Biomolecules. 2022;12(10):1383. doi: 10.3390/biom12101383, PMID 36291594.
5. Dijkshoorn B, Raadsen R, Nurmohamed MT. Cardiovascular disease risk in rheumatoid arthritis anno 2022. J Clin Med. 2022;11(10):2704. doi: 10.3390/jcm11102704, PMID 35628831.
6. Hadwen B, Stranges S, Barra L. Risk factors for hypertension in rheumatoid arthritis patients—A systematic review. Autoimmun Rev. 2021;20(4):102786. doi: 10.1016/j.autrev.2021.102786, PMID 33609791.
7. Pan W, Li Z, Qiu S, Dai C, Wu S, Zheng X, et al. Octahedral Pt-MOF with Au deposition for plasmonic effect and Schottky junction enhanced hydrogen thermal therapy of rheumatoid arthritis. Mater Today Bio. 2022;13:100214. doi: 10.1016/j.mtbio.2022.100214, PMID 35198962.
8. Karstensen JK, Primdahl J, Andersson MLE, Christensen JR, Bremander A. Lifestyle factors in patients with rheumatoid arthritis—a cross-sectional study on two Scandinavian cohorts. Clin Rheumatol. 2022;41(2):387-98. doi: 10.1007/s10067-021-05905-2, PMID 34505213.
9. Kmiołek T, Paradowska-Gorycka A. miRNAs as biomarkers and possible therapeutic strategies in rheumatoid arthritis. Cells. 2022;11(3):452. doi: 10.3390/cells11030452, PMID 35159262.
10. Yerima A, Akintayo R, Adebajo A. Implications of a diagnosis of rheumatoid arthritis in resource-poor countries. Best Pract Res Clin Rheumatol. 2022;36(1):101725. doi: 10.1016/j.berh.2021.101725, PMID 34906416.
11. Elsayed MMA, Aboelez MO, Elsadek BEM, Sarhan HA, Khaled KA, Belal A, et al. Tolmetin sodium fast dissolving tablets for rheumatoid arthritis treatment: preparation and optimization using Box-Behnken design and response surface methodology. Pharmaceutics. 2022 Apr;14(4):880. doi: 10.3390/pharmaceutics14040880, PMID 35456714.
12. Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis. 2012;71(5):638-41. doi: 10.1136/annrheumdis-2011-200990, PMID 22387728.
13. Zaccardelli A, Friedlander HM, Ford JA, Sparks JA. Potential of lifestyle changes for reducing the risk of developing rheumatoid arthritis: is an ounce of prevention worth a pound of cure? Clin Ther. 2019;41(7):1323-45. doi: 10.1016/j.clinthera.2019.04.021, PMID 31196646.
14. Liu X, Tedeschi SK, Barbhaiya M, Leatherwood CL, Speyer CB, Lu B, et al. Impact and timing of Smoking Cessation on reducing risk of rheumatoid arthritis among women in the nurses' health studies. Arthritis Care Res (Hoboken). 2019;71(7):914-24. doi: 10.1002/acr.23837, PMID 30790475.
15. Gan RW, Demoruelle MK, Deane KD, Weisman MH, Buckner JH, Gregersen PK, et al. Omega-3 fatty acids are associated with a lower prevalence of autoantibodies in shared epitope-positive subjects at risk for rheumatoid arthritis. Ann Rheum Dis. 2017;76(1):147-52. doi: 10.1136/annrheumdis-2016-209154, PMID 27190099.
16. Mankia K, Cheng Z, Do T, Hunt L, Meade J, Kang J, et al. Prevalence of periodontal disease and periodontopathic bacteria in anti-cyclic citrullinated protein antibody-positive at-risk adults without arthritis. JAMA Netw Open. 2019;2(6):e195394. doi: 10.1001/jamanetworkopen.2019.5394, PMID 31173126.
17. Polinski KJ, Bemis EA, Feser M, Seifert J, Demoruelle MK, Striebich CC, et al. Perceived stress and

inflammatory arthritis: a prospective investigation in the Studies of the Etiologies of Rheumatoid Arthritis (SERA) cohort. Arthritis Care Res (Hoboken). 2019.
18. Ramos-Remus C, Castillo-Ortiz JD, Aguilar-Lozano L, Padilla-Ibarra J, Sandoval-Castro C, Vargas-Serafin CO, et al. Autoantibodies in prediction of the development of rheumatoid arthritis among healthy relatives of patients with the disease. Arthritis Rheumatol. 2015;67(11):2837-44. doi: 10.1002/art.39297, PMID 26245885 [this ref is also in current prediction model].
19. Kolfenbach JR, Deane KD, Derber LA, O'Donnell C, Weisman MH, Buckner JH, et al. A prospective approach to investigating the natural history of preclinical rheumatoid arthritis (RA) using first-degree relatives of probands with RA. Arthritis Rheum. 2009;61(12):1735-42. doi: 10.1002/art.24833, PMID 19950324.
20. Tanner S, Dufault B, Smolik I, Meng X, Anaparti V, Hitchon C, et al. A prospective study of the development of inflammatory arthritis in the family members of indigenous North American people with rheumatoid arthritis. Arthritis Rheumatol. 2019;71(9):1494-503. doi: 10.1002/art.40880, PMID 30861615.
21. Kim SK, Bae J, Lee H, Kim JH, Park SH, Choe JY. Greater prevalence of seropositivity for anti-cyclic citrullinated peptide antibody in unaffected first-degree relatives in multicase rheumatoid arthritis-affected families. Korean J Intern Med. 2013;28(1):45-53. doi: 10.3904/kjim.2013.28.1.45, PMID 23345996.
22. Gonzalez-Lopez L, Gamez-Nava JI, Jhangri G, Russell AS, Suarez-Almazor ME. Decreased progression to rheumatoid arthritis or other connective tissue diseases in patients with palindromic rheumatism treated with antimalarials. J Rheumatol. 2000;27(1):41-6. PMID 10648016.
23. Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. RMD Open. 2019;5(1):e000870. doi: 10.1136/rmdopen-2018-000870, PMID 31168406.
24. Bos WH, Dijkmans BA, Boers M, van de Stadt RJ, van Schaardenburg D. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: a randomised trial. Ann Rheum Dis. 2010;69(3):571-4. doi: 10.1136/ard.2008.105767, PMID 19363022.
25. Gerlag DM, Safy M, Maijer KI, Tang MW, Tas SW, Starmans-Kool MJF, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study. Ann Rheum Dis. 2018.
26. Strategy to prevent the onset of clinically apparent rheumatoid arthritis (StopRA). NCT02603146. ClinicalTrials.gov [cited May 1 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT02603146.
27. Al-Laith M, Jasenecova M, Abraham S, Bosworth A, Bruce IN, Buckley CD, et al. Arthritis prevention in the pre-clinical phase of RA with abatacept (the APIPPRA study): a multi-centre, randomised, double-blind, parallel-group, placebo-controlled clinical trial protocol. Trials. 2019;20(1):429. doi: 10.1186/s13063-019-3403-7, PMID 31307535.
28. Statins to prevent rheumatoid arthritis (STAPRA) (Netherlands trial register trial NL5036) [cited May 1 2020]. Available from: https://www.trialregister.nl/trial/5036.
29. Treat early arthralgia to reverse or limit impending exacerbation to rheumatoid arthritis (TREAT EARLIER) (Netherlands Trial Register NL4599) [cited May 1 2020]. Available from: https://www.trialregister.nl/trial/4599.
30. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011 Dec 8;365(23):2205-19. doi: 10.1056/NEJMra1004965, PMID 22150039.
31. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010 Sep 25;376(9746):1094-108. doi: 10.1016/S0140-6736(10)60826-4, PMID 20870100.
32. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016 Oct 22;388(10055):2023-38. doi: 10.1016/S0140-6736(16)30173-8, PMID 27156434.
33. Karonitsch T, Smolen JS. The role of natural killer cells in rheumatoid arthritis: a review. Autoimmun Rev. 2020;19(4):102511. doi: 10.1016/j.autrev.2020.102511.
34. Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med. 2015;21(8):895-905. doi: 10.1038/nm.3914, PMID 26214836.
35. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014;506(7488):376-81. doi: 10.1038/nature12873, PMID 24390342.
36. Florescu A, Gherghina FL, Mușetescu AE, Pădureanu V, Roșu A, Florescu MM, et al. Novel biomarkers, diagnostic and therapeutic approach in rheumatoid arthritis interstitial lung disease—A narrative review. Biomedicines. 2022;10(6):1367. doi: 10.3390/biomedicines10061367, PMID 35740390.
37. Dewing KA, Setter SM, Slusher BA. Osteoarthritis and rheumatoid arthritis 2012: pathophysiology, diagnosis, and treatment 2012. In: Nurse practitioner healthcare foundation, ed. Rheumatology: An Annual Review. Philadelphia: Nurse Practitioner Healthcare Foundation; 2012. p. 1-20.
38. Vetchinkina EA, Mikhaylenko DS, Kuznetsova EB, Deryagina TA, Alekseeva EA, Bure IV, et al. Genetic factors of predisposition and clinical characteristics of rheumatoid arthritis in Russian patients. J Pers Med. 2021 Jun;11(6):469. doi: 10.3390/jpm11060469, PMID 34070522.
39. Larid G, Pancarte M, Offer G, Clavel C, Martin M, Pradel V, et al. In rheumatoid arthritis patients, HLA-DRB1*04:01 and rheumatoid nodules are associated with ACPA to a particular fibrin epitope. Front Immunol. 2021;12:692041. doi: 10.3389/fimmu.2021.692041, PMID 34248985.
40. Regueiro C, Casares-Marfil D, Lundberg K, Knevel R, Acosta-Herrera M, Rodriguez-Rodriguez L, et al. HLA-b*08 identified as the most prominently associated major histocompatibility complex locus for anti-carbamylated protein antibody-positive/anti-cyclic citrullinated peptide-negative rheumatoid arthritis. Arthritis Rheumatol. 2021 Jun;73(6):1054-64. doi: 10.1002/art.41538, PMID 33300051.
41. Cai Y, Liang R, Xiao S, Huang Q, Zhu D, Shi GP, et al.. Circ_0088194 Promotes the Invasion and Migration of Rheumatoid Arthritis Fibroblast-Like Synoviocytes via the miR-766-3p/MMP2 Axis. Front Immunol. 2021;12:628654. doi: 10.3389/fimmu.2021.628654, PMID 33692802.

42. Zhi L, Liang J, Huang W, Ma J, Qing Z, Wang XC. Circ_AFF2 facilitates the proliferation and inflammatory response of fibroblast-like synoviocytes in rheumatoid arthritis via the miR-375/TAB2 axis. Exp Mol Pathol. 2021 Mar;119:104617. doi: 10.1016/j.yexmp.2021.104617, PMID 33535081.
43. Luo Z, Chen S, Chen X. CircMAPK9 promotes the progression of fibroblast-like synoviocytes in rheumatoid arthritis via the miR-140-3p/PPM1A axis. J Orthop Surg Res. 2021 Jun 21;16(1):395. doi: 10.1186/s13018-021-02550-y, PMID 34154607.
44. Zitnay JL, Li Y, Qin Z, San BH, Depalle B, Reese SP, et al. Molecular level detection and localization of mechanical damage in collagen enabled by collagen hybridizing peptides. Nat Commun. 2017 Mar;8:14913. doi: 10.1038/ncomms14913, PMID 28327610.
45. Zhang J, Lei H, Li X. LncRNA SNHG14 contributes to proinflammatory cytokine production in rheumatoid arthritis via the regulation of the miR-17-5p/MINK1-JNK pathway. Environ Toxicol. 2021 Dec;36(12):2722-30. doi: 10.1002/tox.23302, PMID 34791664.
46. Xiao J, Wang R, Zhou W, Cai Z, Chen Y, Hu J, et al. LncRNA NEAT1 regulates the proliferation and production of inflammatory cytokines in rheumatoid arthritis fibroblast-like synoviocytes by targeting miR-204-5p. Hum Cell. 2021;34(2):372-82. doi: 10.1007/s13577-020-00467-5, PMID 33389185.
47. Zhang J, Gao FF, Xie J. LRI. 00152/NF-κB feedback loop promotes fibroblast-like synovial cell inflammation in rheumatoid arthritis via regulating miR-103a/TAK1 axis and YY1 expression. Immun Inflam Dis. 2021;9(3):681-93. doi: 10.1002/iid3.418, PMID 34184927.
48. Jiang H, Fan C, Lu Y, Cui X, Liu J. Astragaloside regulates lncRNA LOC100912373 and the miR-17-5p/PDK1 axis to inhibit the proliferation of fibroblast-like synoviocytes in rats with rheumatoid arthritis. Int J Mol Med. 2021;48(1):1-10. doi: 10.3892/ijmm.2021.4963, PMID 34013364.
49. Huang Q, Xu WD, Su LC, Liu XY, Huang AF. Association of CD40 gene polymorphisms with systemic lupus erythematosus and rheumatoid arthritis in a Chinese Han population. Front Immunol. 2021 Apr 22;12:642929. doi: 10.3389/fimmu.2021.642929, PMID 33968033.
50. Chan HC, Wang SC, Lin CH, Lin YZ, Li RN, Yen JH. A novel CD209 polymorphism is associated with rheumatoid arthritis patients in Taiwan. J Clin Lab Anal. 2021;35(5):e23751. doi: 10.1002/jcla.23751, PMID 33792986.
51. Cieśla M, Kolarz B, Majdan M, Darmochwał-Kolarz D. Plasma micro-RNA-22 is associated with disease activity in well-established rheumatoid arthritis. Clin Exp Rheumatol. 2022;40(5):945-51. doi: 10.55563/clinexprheumatol/zdhkrp, PMID 34369363.
52. Hussain MZ, Mahjabeen I, Khan MS, Mumtaz N, Maqsood SU, Ikram F, et al. Genetic and expression deregulation of immunoregulatory genes in rheumatoid arthritis. Mol Biol Rep. 2021 Jun;48(6):5171-80. doi: 10.1007/s11033-021-06518-3, PMID 34196898.
53. Hosseini N, Tahoori MT, Mohammadzadeh A, Zarei Jaliani H, Bitaraf Sani M, Soleimani Salehabadi H. IRAK1 gene polymorphism in rheumatoid arthritis. Immunol Investig. 2021;50(2-3):304-21. doi: 10.1080/08820139.2020.1764028, PMID 32507051.
54. Liu X, Peng L, Li D, He C, Xing S, Wang Y, et al. The impacts of IL1R1 and IL1R2 genetic variants on rheumatoid arthritis risk in the Chinese Han population: A case-control study. Int J Gen Med. 2021;14:2147-59. doi: 10.2147/IJGM.S291395, PMID 34093035.
55. Xie Q, Xu WD, Pan M, Lan YY, Liu XY, Su LC et al. Association of IL-35 expression and gene polymorphisms in rheumatoid arthritis. Int Immunopharmacol. 2021 Feb;90:107231. doi: 10.1016/j.intimp.2020.107231. PMID 33307515.
56. Hao Y, Xie L, Xia J, Liu Z, Yang B, Zhang M. Plasma interleukin-21 levels and genetic variants are associated with susceptibility to rheumatoid arthritis. BMC Musculoskelet Disord. 2021;22(1):1-9. doi: 10.1186/s12891-021-04571-1, PMID 34344450.
57. Firestein GS, Zvaifler NJ. How important are T cells in chronic rheumatoid synovitis?: II. T cell-independent mechanisms from beginning to end. Arthritis Rheum. 2002;46(2):298-308. doi: 10.1002/art.502, PMID 11840432.
58. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously—predictive markers, socioeconomic status, and comorbidity. J Rheumatol. 1986;13(5):841-5. PMID 3820193.
59. Yelin E, Wanke LA. An assessment of the annual and long-term direct costs: the impact of poor function and functional decline. Arthritis Rheum. 1999;42(6):1209-18. doi: 10.1002/1529-0131(199906)42:6<1209::AID-ANR18>3.0.CO;2-M, PMID 10366114.
60. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide rheumatoid arthritis investigators group. Arch Intern Med. 1999;159(21):2542-50. doi: 10.1001/archinte.159.21.2542, PMID 10573044.
61. Kremer JM, Genovese MC, Cannon GW, Caldwell JR, Cush JJ, Furst DE, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002;137(9):726-33. doi: 10.7326/0003-4819-137-9-200211050-00007, PMID 12416946.
62. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35. doi: 10.1002/art.1780380602.
63. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. N Engl J Med. 2000;343(22):1594-602. doi: 10.1056/NEJM200011303432202, PMID 11096166.
64. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human Antitumor Necrosis Factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35-45. doi: 10.1002/art.10697, PMID 12528101.
65. Blumenauer B, Judd M, Cranney A, Burls A, Coyle D, Hochberg M, et al. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2003;4(4):CD004525. doi: 10.1002/14651858.CD004525, PMID 14584021.

66. Humira (adalimumab) [package insert]. Abbott Park, IL: Abbott Laboratories [cited Dec 7, 2004]. Available from: http://fda.gov/cder/foi/label/2002/adalabb123102LB.htm#clin.
67. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatol (Oxf Engl). 2003;42(5):617-21. doi: 10.1093/rheumatology/keg263, PMID 12709536.
68. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med. 2004;350(21):2167-79. doi: 10.1056/NEJMra032906, PMID 15152062.
69. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Bijl H, et al. Repeated therapy with monoclonal antibody to tumor necrosis factor α (cA2) in patients with rheumatoid arthritis. Lancet. 1994;344(8930):1125-7. doi: 10.1016/s0140-6736(94)90632-7, PMID 7934495.
70. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of antitumor necrosis factor a monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41(9):1552-63. doi: 10.1002/1529-0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W, PMID 9751087.
71. Shingu M, Nagai Y, Isayama T, Naono T, Nobunaga M, Nagai Y. The effects of cytokines on metalloproteinase inhibitors (TIMP) and collagenase production by human chondrocytes and TIMP production by synovial cells and endothelial cells. Clin Exp Immunol. 1993;94(1):145-9. doi: 10.1111/j.1365-2249.1993.tb05992.x, PMID 8403497.
72. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum. 2002;46(2):328-46. doi: 10.1002/art.10148, PMID 11840435.
73. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum. 1998;41(12):2196-204. doi: 10.1002/1529-0131(199812)41:12<2196::AID-ART15>3.0.CO;2-2, PMID 9870876.
74. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46(3):614-24. doi: 10.1002/art.10141, PMID 11920396.
75. Fleischmann RM, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003;48(4):927-34. doi: 10.1002/art.10870, PMID 12687534.
76. Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, et al. A multicentre, double-blind, randomised, placebo-controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004;63(9):1062-8. doi: 10.1136/ard.2003.016014, PMID 15082469.
77. Yang BB, Baughman S, Sullivan JT. Pharmacokinetics of anakinra in subjects with different levels of renal function. Clin Pharmacol Ther. 2003;74(1):85-94. doi: 10.1016/S0009-9236(03)00094-8, PMID 12844139.
78. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell co-stimulation. Annu Rev Immunol. 1996;14:233-58. doi: 10.1146/annurev.immunol.14.1.233, PMID 8717514.
79. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med. 2003;349(20):1907-15. doi: 10.1056/NEJMoa035075, PMID 14614165.
80. Kremer J, Shergy W, Tindall E, et al. Sustained clinical efficacy demonstrated by the selective co-stimulation modulator abatacept (CTLA4Ig) in combination with methotrexate at 2 years in rheumatoid arthritis patients with an inadequate response to methotrexate. Abstract presented at 68th Annual Scientific Meeting. the American College of Rheumatology. San Antonio: Tex; Oct 16-21, 2004:Abstract S351.
81. Dougados M, Westhovens R, Williams St Clair E, et al. Sustained remission and major clinical response at 2 years shown with abatacept (CTLA4Ig) in combination with methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate. Abstract presented at 68th Annual Scientific Meeting. the American College of Rheumatology. San Antonio: Tex; Oct 16-21, 2004:Abstract S359.
82. Moreland L, Weisman M, Alten R, et al. Abatacept (CTLA4Ig) in combination with methotrexate for the treatment of rheumatoid arthritis: favorable safety and tolerability profile sustained over 2 years. Abstract presented at 68th Annual Scientific Meeting. the American College of Rheumatology. San Antonio: Tex; Oct 16-21, 2004:Abstract S1475.
83. Kremer J, Westhovens R, Moreland L, et al. Efficacy and safety of the selective co-stimulation modulator abatacept with methotrexate for treating rheumatoid arthritis: 1-year clinical and radiographic results from the phase 3 AIM (abatacept in Inadequate responders to methotrexate) Trial. In: Program book supplement: late breaking and fellow. Abstracts of the American college of rheumatology 68th annual scientific meeting. San Antonio: Tex; Oct 16-21, 2004:Abstract L2.
84. Edwards JCW, Cambridge G. Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. Rheumatology (Oxford). 2001;40(2):205-11. doi: 10.1093/rheumatology/40.2.205, PMID 11257159.
85. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994;83(2):435-45, PMID 7506951.
86. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572-81. doi: 10.1056/NEJMoa032534, PMID 15201414.
87. Stahl HD, Szczepanski L, Szechinski J, et al. Rituximab in rheumatoid arthritis: efficacy and safety from a

randomised controlled trial. Ann Rheum Dis. 2003;62;Suppl:0P004.
88. Nishimoto N, Kishimoto T, Yoshizaki K. Anti-interleukin 6 receptor antibody treatment in rheumatic disease. Ann Rheum Dis. 2000;59;Suppl 1:i21-7. doi: 10.1136/ard.59.suppl_1.i21, PMID 11053081.
89. Madhok R, Crilly A, Watson J, Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. Ann Rheum Dis. 1993;52(3):232-4. doi: 10.1136/ard.52.3.232, PMID 8484679.
90. Sato K, Tsuchiya M, Saldanha J, Koishihara Y, Ohsugi Y, Kishimoto T, et al. Reshaping a human antibody to inhibit the interleukin 6-dependent tumor cell growth. Cancer Res. 1993;53(4):851-6. PMID 8428365.
91. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2004;50(6):1761-9. doi: 10.1002/art.20303, PMID 15188351.
92. Maini RN, Taylor PC, Pavelka K, et al. Efficacy of IL-6 receptor antagonist MRA in rheumatoid arthritis patients with an incomplete response to methotrexate (CHARISMA). RA: randomized clinical trials. Abstract presented at 67th Annual Scientific Meeting. the American College of Rheumatology. Orlando: Fla; Oct 23-28, 2003:Abstract S1704.
93. Harris ED. Clinical features of rheumatoid arthritis. In: Ruddy S, Harris ED, Sledge CB, Kelley WN, editors. Kelley's textbook of rheumatology. 7th ed. Philadelphia: W B Saunders; 2005. p. 1043-78.
94. Akil M, Amos RS. ABC of rheumatology. Rheumatoid arthritis—I: clinical features and diagnosis. BMJ. 1995;310(6979):587-90. doi: 10.1136/bmj.310.6979.587, PMID 7888939.
95. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24. doi: 10.1002/art.1780310302, PMID 3358796.
96. Saraux A, Berthelot JM, Chalès G, Le Henaff C, Thorel JB, Hoang S, et al. Ability of the American College of Rheumatology 1987 criteria to predict rheumatoid arthritis in patients with early arthritis and classification of these patients two years later. Arthritis Rheum. 2001;44(11):2485-91. doi: 10.1002/1529-0131(200111)44:11<2485::aid-art428>3.0.co;2-s, PMID 11710704.
97. Scottish Intercollegiate Guidelines Network. Management of early rheumatoid arthritis; Dec 2000. SIGN No. 48 [cited Jul 19, 2005]. Available from: http://www.sign.ac.uk/guidelines/fulltext/48/index.html.
98. Lin C-Y, Nguyen UTN, Hsieh H-Y, Tahara H, Chang Y-S, Wang B-Y, et al. Peptide-based electrochemical sensor with nanogold enhancement for detecting rheumatoid arthritis. Talanta. 2022 Jan 15;236:122886. doi: 10.1016/j.talanta.2022.122886, PMID 34736325.
99. Morales-Ivorra I, González-Pérez S, Garrido-Castro JL, et al. Automatic detection of inflamed joints in rheumatoid arthritis using thermography and machine learning. PLOS ONE. 2020;15(9):e0238987. doi: 10.1371/journal.pone.0238987.
100. Nasra S, Bhatia DD, Kumar A. Recent advances in nanoparticle-based drug delivery system for rheumatoid arthritis Treatment 2022. Nanoscale Adv.
101. Pathade V, Nene S, Ratnam S, Khatri DK, Raghuvanshi RS, Singh SB, et al. Emerging insights of peptide-based nanotherapeutics for effective management of rheumatoid arthritis. Life Sci. 2023;312:121257. doi: 10.1016/j.lfs.2022.121257, PMID 36462722.
102. Elkomy MH, Alruwaili NK, Elmowafy M, Shalaby K, Zafar A, Ahmad N, et al. Surface-Modified Bilosomes nanogel bearing a natural plant alkaloid for safe management of rheumatoid arthritis inflammation. Pharmaceutics. 2022 Mar;14(3):563. doi: 10.3390/pharmaceutics14030563, PMID 35335939.
103. Prasad B, McGeough C, Eakin A, Ahmed T, Small D, Gardiner P, et al. ATRPred: A machine learning-based tool for clinical decision-making of anti-TNF treatment in rheumatoid arthritis patients. PLOS Comp Biol. 2022;18(7):e1009542. doi: 10.1371/journal.pcbi.1009542, PMID 34329353.
104. Mane RR, Kale PP. The roles of HDAC with IMPDH and mTOR with JAK as future targets in the treatment of rheumatoid arthritis with combination therapy. J Complement Integr Med. 2022 Oct 4;20(1):11-20. doi: 10.1515/jcim-2022-0114, PMID 36409592.
105. Chen MS, Sitorus MA, Kuo CH, Kuo WW, Chen TS, Fu CY et al. Epigallocatechin-3-gallate pretreatment improves autologous adipose-derived stem cells against rheumatoid arthritis-induced neuroinflammation in the brain of collagen-induced rats. Neurotox Res. 2022;40(5):1223-34. doi: 10.1007/s12640-022-00406-9, PMID 34934771.
106. Meng X, Zhang X, Su X, Liu X, Ren K, Ning C, et al. Daphnes Cortex and its licorice-processed products suppress inflammation via the TLR4/NF-κB/NLRP3 signaling pathway and regulation of the metabolic profile in the treatment of rheumatoid arthritis. J Ethnopharmacol. 2022;283:114657. doi: 10.1016/j.jep.2021.114657, PMID 34600080.
107. Pham DT, Thao NTP, Thuy BTP, Van De T, Nguyen TQC, Nguyen NN. Thao Silk fibroin hydrogel containing Sesbania sesban L. extract for rheumatoid arthritis treatment. Drug Deliv. 2022;29(1):882-8. doi: 10.1080/10717544.2022.2008131, PMID 35453909.
108. Sánchez-Laulhé P, Luque-Romero LG, Barrero-García FJ, Biscarri-Carbonero A, Ángela JMIR mHealth uHealth, Blanquero J, Suero-Pineda A, Heredia-Rizo AM, et al. An Exercise and Educational and Self-management Program Delivered With a Smartphone App (CareHand) in Adults With Rheumatoid Arthritis of the Hands: Randomized Controlled Trial. JMIR mHealth uHealth. 2022 Apr 14;10(4):e35462. doi: 10.2196/35462. PMID: 34884101.
109. Bruno MC, Cristiano MC, Celia C, d'Avanzo N, Mancuso A, Paolino D, et al. Injectable drug delivery systems for osteoarthritis and rheumatoid arthritis. ACS Nano. 2022;16(12):19665-90. doi: 10.1021/acsnano.2c06393, PMID 36512378.
110. Nornberg AB, Martins CC, Cervi VF, Sari MHM, Cruz L, Luchese EA et al. Transdermal release of methotrexate by cationic starch/poly (vinyl alcohol)-based films as an approach for rheumatoid arthritis treatment. Int J Pharm. 2022;611:121285. doi: 10.1016/j.ijpharm.2021.121285, PMID 34610339.
111. Feng Z, Fu L, Wang J, Zhu Y, He X, Zhou L, et al. Efficacy of Tripterygium glycosides (TG) in rheumatoid

arthritis as a disease-modifying anti-rheumatic drug (DMARD) in combination with conventional DMARDs: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2022;184:106405. doi: 10.1016/j.phrs.2022.106405, PMID 36028187.
112. Pelechas E, Drosos AA. State-of-the-art glucocorticoid-targeted drug therapies for the treatment of rheumatoid arthritis. Expert Opin Pharmacother. 2022;23(6):703-11. doi: 10.1080/14656566.2022.2049238, PMID 35313795.
113. Ben Mrid RB, Bouchmaa N, Ainani H, El Fatimy R, Malka G, Mazini L. Anti-rheumatoid drug advancements: new insights into the molecular treatment of rheumatoid arthritis. Biomed Pharmacother. 2022 Oct;151:113126. doi: 10.1016/j.biopha.2022.113126. PMID 35643074.
114. Li X, Wang H, Zou X, Su H, Li C. Methotrexate-loaded folic acid of solid-phase synthesis conjugated gold nanoparticles targeted treatment for rheumatoid arthritis. Eur J Pharm Sci. 2022;170:106101. doi: 10.1016/j.ejps.2021.106101, PMID 34936935.
115. Jaaffer MD, Al-Ogaidi IAZ, Zaidan ZA. Developing gold-resveratrol nanoconjugates for management of rheumatoid arthritis (RA). Egypt J Hosp Med. 2022;89(2):6637-45. doi: 10.21608/ejhm.2022.270744.
116. Kofoed Andersen C, Khatri S, Hansen J, Slott S, Pavan Parvathaneni R, Mendes AC, et al. Carbon nanotubes-potent carriers for targeted drug delivery in rheumatoid arthritis. Pharmaceutics. 2021 Apr 1;13(4):453. doi: 10.3390/pharmaceutics13040453, PMID 33801590.
117. Marasini N, Er G, Fu C, Subasic CN, Ibrahim J, Skwarczynski M et al. Development of a hyperbranched polymer-based methotrexate nanomedicine for rheumatoid arthritis. Acta Biomater. 2022;142:298-307. doi: 10.1016/j.actbio.2022.01.054, PMID 35114374.
118. Yu C, Liu H, Guo C, Chen Q, Su Y, Guo H et al. Dextran sulfate-based MMP-2 enzyme-sensitive SR-A receptor targeting nanomicelles for the treatment of rheumatoid arthritis. Drug Deliv. 2022;29(1):454-65. doi: 10.1080/10717544.2022.2032482, PMID 35119317.
119. He Y, Xin Y, Rosas EC, Alencar LMR, Santos-Oliveira R, Peng X, et al. Engineered high-loaded mixed-monoclonal antibodies (adalimumab, rituximab and trastuzumab) polymeric nanoparticle for rheumatoid arthritis treatment: A proof of concept. J Biomed Nanotechnol. 2020 Aug 1;16(8):1254-66. doi: 10.1166/jbn.2020.2966, PMID 33397555.
120. Chen H, Sun Y, Xu X, Ye Q. Targeted delivery of methotrexate by modified yeast β-glucan nanoparticles for rheumatoid arthritis therapy. Carbohydr Polym. 2022 Nov 1;284:119183. doi: 10.1016/j.carbpol.2022.119183. PMID 35287902.
121. Zhao YP, Han JF, Zhang FY, Liao TT, Na R, Yuan XF, et al. Flexible nano-liposomes-based transdermal hydrogel for targeted delivery of dexamethasone for rheumatoid arthritis therapy. Drug Deliv. 2022;29(1):2269-82. doi: 10.1080/10717544.2022.2096718, PMID 35815790.
122. Mohammadi G, Korani M, Nemati H, Nikpoor AR, Rashidi K, Varmira K, et al. Crocin-loaded nanoliposomes: preparation, characterization, and evaluation of anti-inflammatory effects in an experimental model of adjuvant-induced arthritis. J Drug Deliv Sci Technol. 2022;74:103618. doi: 10.1016/j.jddst.2022.103618.
123. Morales-Ivorra I, Narváez J, Gómez-Vaquero C, Moragues C, Nolla JM, Narváez JA et al. Assessment of inflammation in patients with rheumatoid arthritis using thermography and machine learning: a fast and automated technique. RMD Open. 2022;8(2):e001963. doi: 10.1136/rmdopen-2021-001963, PMID 35195387.
124. Taylor PC. The value of sensitive imaging modalities in rheumatoid arthritis. Arthritis Res Ther. 2003;5(5):1-4. doi: 10.1186/ar903, PMID 14519205.
125. Chi Z, Huang L, Wu D, Long X, Xu X, Jiang H. First assessment of thermoacoustic tomography for in vivo detection of rheumatoid arthritis in the finger joints detection of rheumatoid arthritis in the finger joints. Med Phys. 2022;49(1):84-92. doi: 10.1002/mp.15340, PMID 34767650.
126. Huang Y, Liu KJ, Chen GW, Liu JF, Mo FQ, Xie YH. Diagnostic value of semi-quantitative grading of musculoskeletal ultrasound in wrist and hand lesions of subclinical synovitis in rheumatoid arthritis. Am J Nucl Med Mol Imaging. 2022;12(1):25-32. PMID 35295888.
127. Burska AN, Boissinot M, Ponchel F, Vital EM. New strategies for diagnosis and management of rheumatoid arthritis. Rheumatology. 2014;53(1):3-15. doi: 10.1093/rheumatology/ket301.
128. Zhang X, Zhang X, Yang Y, Zhi K, Chen Y, Zhao J, et al. Association between passive smoking and the risk of rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol. 2022;41(1):1-18. doi: 10.1007/s10067-021-05805-5, PMID 34218393.
129. Nasra S, Bhatia DD, Kumar A. Recent advances in nanoparticle-based drug delivery system for rheumatoid arthritis Treatment 2022. Nanoscale Adv.
130. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis. 2002;61(4):290-7. doi: 10.1136/ard.61.4.290, PMID 11874828.
131. Keystone EC, Breedveld FC, van der Heijde D, Landewé R, Florentinus S, Arulmani U, et al. Longterm effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. J Rheumatol. 2014;41(1):5-14. doi: 10.3899/jrheum.130543, PMID 24241487.
132. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381(9877):1541-50. doi: 10.1016/S0140-6736(13)60250-0.
133. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507. doi: 10.1056/NEJMoa1109071, PMID 22873530.
134. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144(12):865-76. doi: 10.7326/0003-4819-144-12-200606200-00003, PMID 16785475.

135. Edwards JC, Szczepański L, Szechiński J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572-81. doi: 10.1056/NEJMoa032534, PMID 15201414.
136. Fleischmann RM, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003;48(4):927-34. doi: 10.1002/art.10870, PMID 12687534.
137. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382(9894):780-9. doi: 10.1016/S0140-6736(13)60594-2, PMID 23769296.
138. Rader RA. (Re)defining biopharmaceutical. Nat Biotechnol. 2008;26(7):743-51. doi: 10.1038/nbt0708-743, PMID 18612293.
139. Rantapää-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2003;48(10):2741-9. doi: 10.1002/art.11223, PMID 14558078.
140. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004;50(2):380-6. doi: 10.1002/art.20018, PMID 14872479.
141. Sokolove J, Bromberg R, Deane KD, Lahey LJ, Derber LA, Chandra PE, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis. PLOS ONE. 2012;7(5):e35296. doi: 10.1371/journal.pone.0035296, PMID 22662108.
142. Deane KD, O'Donnell CI, Hueber W, Majka DS, Lazar AA, Derber LA, et al. The number of elevated cytokines and chemokines in preclinical seropositive rheumatoid arthritis predicts time to diagnosis in an age-dependent manner. Arthritis Rheum. 2010;62(11):3161-72. doi: 10.1002/art.27638, PMID 20597112.
143. Van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann Rheum Dis. 2013;72(12):1920-6. doi: 10.1136/annrheumdis-2012-202127, PMID 23178208.
144. Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Ann Rheum Dis. 2015;74(9):1659-66. doi: 10.1136/annrheumdis-2014-205227, PMID 24728331.
145. Burgers LE, Raza K, van der Helm-van Mil AH. Prospective study of subjects with arthralgia: development of classification criteria for clinically suspect arthralgia of recent onset. Ann Rheum Dis. 2017;76(3):477-85.
146. Ramos-Remus C, Castillo-Ortiz JD, Aguilar-Lozano L, et al. Unaffected first-degree relatives of patients with rheumatoid arthritis show autoimmunity and a reduced number of natural killer cells. J Rheumatol. 2015;42(10):1829-35.
147. de Hair MJH, van de Sande MGH, Ramwadhdoebe TH, et al. Features of the synovium of individuals at risk of developing rheumatoid arthritis: implications for understanding preclinical rheumatoid arthritis. Arthritis Rheum. 2013;65(2):269-75.