REVIEW ARTICLE

To study the pathogenic causes and contemporary pharmaceutical treatments for rheumatoid arthritis: A systematic review

[1]Dr. Prahlad Kumar, [2]Dr. Pravas Kumar, [3]Dr. Abhishek, [4]Dr. Dilip Kumar Chudhry

[1,2,3]Senior Resident, [4]Assistant Professor, ANMMCH Gaya, Bihar, India

Corresponding author
Dr. Dilip Kumar Chudhry
Assistant Professor, ANMMCH Gaya, Bihar, India

Received: 22 February, 2024 Accepted: 29 March, 2024

ABSTRACT

Background: The development of RA is influenced by an intricate combination of genetic, environmental, and immunological variables, resulting in persistent inflammation and damage to the joints. The development of the illness is influenced by genetic predisposition, namely involving HLA-DRB1 and other susceptibility genes, as well as environmental triggers including smoking and infections. Rheumatoid arthritis (RA) is characterized by chronic inflammation, which is caused by the activation of both innate and adaptive immune cells in an uncontrolled manner. The inflammatory response and joint degradation are mediated by important cytokines such as TNF-α, IL-1, and IL-6, as well as intracellular signaling pathways including NF-κB, JAK-STAT, and MAPK. Effector cells, such as synovial fibroblasts, osteoclasts, and chondrocytes, have significant involvement in the degenerative processes of rheumatoid arthritis (RA). Comprehending these pathways has resulted in the creation of focused treatments that have greatly improved the control of RA. This thorough review examines the development of pharmacologic treatments for rheumatoid arthritis, focusing on the shift from conventional disease-modifying antirheumatic drugs (DMARDs) to biologic medications and the rise of Janus kinase (JAK) inhibitors.

Materials and method:A systematic review was conducted during June 2021 to July 2022 using the MeSH Terms rheumatoid arthritis, inflammatory disorders, immunologic bone disorders. Pubmed, Scopus, Embase and google scholar databases were also searched with the same search strategy and the references of selected journals were scanned to try to find more studies.

Conclusion: The pathogenesis of RA involves a complex interplay of genetic, environmental, and immunological factors that lead to chronic inflammation and joint destruction. Genetic predisposition, particularly involving HLA-DRB1 and other susceptibility genes, and environmental triggers such as smoking and infections, set the stage for the disease. The dysregulated immune response, characterized by the activation of innate and adaptive immune cells, drives the chronic inflammation seen in RA. Key cytokines such as TNF-α, IL-1, and IL-6, along with intracellular signaling pathways like NF-κB, JAK-STAT, and MAPK, mediate the inflammatory response and joint destruction. Effector cells, including synovial fibroblasts, osteoclasts, and chondrocytes, play crucial roles in the pathological mechanisms of RA. Understanding these mechanisms has led to the development of targeted therapies that have significantly improved the management of RA.This comprehensive overview covers the evolution of pharmacologic therapies for rheumatoid arthritis, highlighting the transition from traditional DMARDs to biologic agents and the emergence of JAK inhibitors.

Keywords: Pathogenic causes, Contemporary pharmaceutical treatments, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that primarily affects the synovial joints, leading to progressive joint destruction, disability, and reduced quality of life. It is a multifactorial disease with genetic, environmental, and immunological contributions. The disease affects about 0.5-1% of the global population, with a higher prevalence in women compared to men. This introduction aims to provide an overview of RA, discussing its epidemiology, pathophysiology, clinical manifestations, diagnostic criteria, and current treatment strategies[1].

Materials and method:
A systematic review was conducted during June 2021 to July 2022using the MeSH Terms rheumatoid arthritis, inflammatory disorders, immunologic bone disorders. Pubmed, Scopus, Embase and google scholar databases were also searched with the same search strategy and the references of selected journals were scanned to try to find more studies.

Epidemiology
RA is one of the most common autoimmune diseases, with significant variations in prevalence across different populations and geographic regions. The prevalence is higher in developed countries, particularly in Northern Europe and North America, compared to Asian and African countries . The onset of RA typically occurs between the ages of 30 and 60, although it can affect individuals at any age. Women are approximately three times more likely to develop RA than men, a disparity attributed to hormonal and genetic factors[2].

Pathophysiology
The exact etiology of RA remains unclear, but it is widely accepted that a combination of genetic predisposition and environmental triggers initiates the disease process. Genetic factors account for about 50-60% of the risk of developing RA. The strongest genetic association is with the HLA-DRB1 gene, specifically the shared epitope alleles, which are found in up to 80% of RA patients . Other genetic factors, including PTPN22, STAT4, and TNFAIP3, have also been implicated in RA susceptibility.
Environmental factors such as smoking, infections, and hormonal influences play a crucial role in triggering RA in genetically predisposed individuals. Smoking is the most well-established environmental risk factor, increasing the risk of RA, particularly in individuals carrying the HLA-DRB1 shared epitope . Periodontal disease, caused by Porphyromonasgingivalis, has also been associated with an increased risk of RA due to its role in citrullination, a process that leads to the formation of anti-citrullinated protein antibodies (ACPAs).
The pathogenesis of RA involves a complex interplay between the innate and adaptive immune systems. Synovial inflammation is characterized by the infiltration of immune cells, including macrophages, T cells, B cells, and dendritic cells, into the synovium. These cells release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which drive the inflammatory response and promote synovial hyperplasia and pannus formation. The presence of ACPAs and rheumatoid factor (RF), which target citrullinated proteins and IgG, respectively, are hallmarks of RA and are associated with more severe disease[3].

Mechanism of pathology of RA
Genetic Predisposition
Genetic factors play a significant role in the susceptibility to RA. Family and twin studies have demonstrated a strong genetic component, with heritability estimates ranging from 50% to 60% . The most well-established genetic risk factor for RA is the presence of specific alleles in the human leukocyte antigen (HLA) region, particularly the HLA-DRB1 gene. The shared epitope hypothesis suggests that certain HLA-DRB1 alleles encode a common amino acid sequence in the third hypervariable region of the HLA-DR molecule, which predisposes individuals to RA [3]. These alleles are found in approximately 60-70% of RA patients, compared to 20-30% of the general population [4].
Other non-HLA genes have also been implicated in RA susceptibility. Genome-wide association studies (GWAS) have identified over 100 genetic loci associated with RA, including PTPN22, STAT4, TRAF1/C5, and PADI4 [5]. PTPN22 encodes a protein tyrosine phosphatase involved in T cell receptor signaling, and its polymorphisms are associated with increased risk of RA [6]. STAT4 is involved in cytokine signaling and differentiation of T helper cells, and its variants are linked to RA and other autoimmune diseases [7]. TRAF1/C5 is involved in TNF receptor signaling and has been associated with RA severity and progression [8]. PADI4 encodes peptidyl arginine deiminase, an enzyme involved in the citrullination of proteins, a process implicated in the generation of autoantibodies in RA [9].

Environmental Triggers
Environmental factors, in conjunction with genetic predisposition, are crucial in the onset of RA. Among these factors, smoking is the most well-documented environmental risk factor for RA, particularly in individuals with the HLA-DRB1 shared epitope [10]. Smoking is thought to promote the citrullination of proteins in the lungs, leading to the production of anti-citrullinated protein antibodies (ACPAs) [11]. These autoantibodies are present in up to 70-80% of RA patients and are associated with more severe disease [12].
Infections have also been proposed as environmental triggers of RA. Molecular mimicry, where microbial antigens share structural similarities with host antigens, can lead to an autoimmune response. For example, Porphyromonasgingivalis, a bacterium associated with periodontal disease, expresses an enzyme that citrullinates host proteins, potentially triggering the production of ACPAs [13]. Epstein-Barr virus (EBV) has also been implicated in RA due to its ability to infect B cells and induce the production of autoantibodies [14].

Immune System Dysregulation

The pathogenesis of RA involves a dysregulated immune response characterized by the activation of both the innate and adaptive immune systems. The synovium, the primary site of inflammation in RA, becomes infiltrated with a variety of immune cells, including macrophages, T cells, B cells, dendritic cells, and neutrophils. These cells interact in a complex network, leading to chronic inflammation and joint damage.

Innate Immune System

The innate immune system plays a critical role in the initiation and perpetuation of synovial inflammation in RA. Synovial macrophages and dendritic cells are key players in this process. Activated macrophages produce pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are central to the inflammatory cascade in RA [15]. These cytokines promote the recruitment and activation of other immune cells, perpetuating the inflammatory response.

Neutrophils, the most abundant immune cells in the synovial fluid of RA patients, contribute to inflammation by releasing reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs) [16]. NETs can expose citrullinated proteins to the immune system, further promoting autoantibody production [17].

Adaptive Immune System

The adaptive immune system, particularly T and B lymphocytes, plays a crucial role in the pathogenesis of RA. CD4+ T helper (Th) cells, particularly Th1 and Th17 subsets, are abundant in the RA synovium. Th1 cells produce interferon-gamma (IFN-γ), which activates macrophages and enhances the production of pro-inflammatory cytokines [18]. Th17 cells produce interleukin-17 (IL-17), a cytokine that drives inflammation by promoting the production of other pro-inflammatory cytokines and matrix metalloproteinases (MMPs) [19].

B cells contribute to RA pathology through the production of autoantibodies, such as RF and ACPAs, and by presenting antigens to T cells. The formation of immune complexes between autoantibodies and their antigens leads to the activation of the complement system, further driving inflammation [20]. Additionally, B cells can produce pro-inflammatory cytokines, such as TNF-α and IL-6, and play a role in ectopic lymphoid neogenesis within the synovium [21].

Molecular Pathways in RA

The chronic inflammation and joint destruction in RA are mediated by a complex network of molecular pathways involving cytokines, signaling molecules, and effector cells.

Cytokine Signaling

Cytokines are key mediators of the inflammatory response in RA. TNF-α, IL-1, and IL-6 are the most well-studied cytokines in RA and are central to its pathogenesis.

1. **TNF-α:** TNF-α is a pro-inflammatory cytokine produced primarily by macrophages and T cells. It promotes inflammation by inducing the production of other cytokines (IL-1, IL-6), chemokines, and adhesion molecules, leading to the recruitment and activation of immune cells [22]. TNF-α also stimulates the production of MMPs and other enzymes that degrade the extracellular matrix, contributing to joint destruction [23]. The pivotal role of TNF-α in RA pathogenesis is evidenced by the efficacy of TNF inhibitors in treating RA [24].
2. **IL-1:** IL-1 is produced by macrophages, synovial fibroblasts, and other cells in the RA synovium. It contributes to inflammation by inducing the expression of adhesion molecules, chemokines, and MMPs [25]. IL-1 also stimulates the production of prostaglandins and nitric oxide, which mediate pain and further inflammation [26].
3. **IL-6:** IL-6 is a multifunctional cytokine produced by various cells, including macrophages, T cells, and synovial fibroblasts. It promotes inflammation by inducing the differentiation of Th17 cells and the production of acute-phase reactants [27]. IL-6 also plays a role in B cell differentiation and the production of autoantibodies [28].

Signaling Pathways

Several intracellular signaling pathways are involved in the inflammatory response and joint destruction in RA.

1. **NF-κB Pathway:** The nuclear factor kappa B (NF-κB) pathway is a critical regulator of inflammation and immune responses in RA. NF-κB is activated by various stimuli, including TNF-α and IL-1, leading to the transcription of pro-inflammatory genes [29]. Inhibition of the NF-κB pathway has been shown to reduce inflammation and joint damage in experimental models of RA [30].
2. **JAK-STAT Pathway:** The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is involved in cytokine signaling in RA. Cytokines such as IL-6 and interferons activate JAKs, which phosphorylate STATs, leading to their dimerization and translocation to the nucleus to regulate gene expression [31]. JAK inhibitors, such as tofacitinib and baricitinib, have been developed as targeted therapies for RA [32].
3. **MAPK Pathway:** The mitogen-activated protein kinase (MAPK) pathway is activated by various cytokines and stress signals, leading to the

phosphorylation and activation of transcription factors involved in inflammation and apoptosis [33]. Inhibition of the MAPK pathway has been shown to reduce inflammation and joint damage in RA [34].

Effector Cells

Several cell types contribute to the chronic inflammation and joint destruction in RA.

1. **Synovial Fibroblasts:** Synovial fibroblasts are key effector cells in RA, producing pro-inflammatory cytokines, chemokines, and MMPs that contribute to inflammation and joint destruction [35]. These cells also exhibit aggressive behavior, invading and degrading cartilage and bone [36]. Targeting synovial fibroblasts and their signaling pathways is a potential therapeutic strategy in RA [37].
2. **Osteoclasts:** Osteoclasts are bone-resorbing cells that play a crucial role in the joint destruction seen in RA. The differentiation and activation of osteoclasts are regulated by the receptor activator of nuclear factor kappa-B ligand (RANKL) and its receptor RANK [38]. Synovial fibroblasts and T cells in the RA synovium produce RANKL, promoting osteoclastogenesis and bone resorption [39]. Inhibition of the RANKL pathway, such as with the monoclonal antibody denosumab, has been shown to reduce bone erosion in RA [40].
3. **Chondrocytes:** Chondrocytes are the resident cells of cartilage and play a role in maintaining cartilage integrity. In RA, chondrocytes are exposed to pro-inflammatory cytokines, leading to the production of MMPs and other catabolic enzymes that degrade cartilage [41]. Chondrocyte apoptosis and reduced anabolic activity further contribute to cartilage destruction [42].

Clinical Manifestations

RA primarily affects the synovial joints, leading to symmetric polyarthritis. The small joints of the hands, wrists, and feet are typically involved early in the disease, followed by larger joints such as the knees, hips, and shoulders. Patients often present with pain, swelling, and stiffness in the affected joints, particularly in the morning or after periods of inactivity (morning stiffness). As the disease progresses, joint deformities such as ulnar deviation, swan-neck deformity, and boutonniere deformity may develop due to chronic inflammation and joint damage.Extra-articular manifestations of RA are common and can affect various organ systems, including the skin, eyes, lungs, heart, and blood vessels. Rheumatoid nodules, which are firm, subcutaneous nodules typically found over bony prominences, are the most characteristic extra-articular feature of RA . Ocular involvement may include keratoconjunctivitissicca (dry eyes) and scleritis. Pulmonary manifestations, such as interstitial lung disease and pleuritis, are also observed in a subset of patients . Cardiovascular disease is a major cause of morbidity and mortality in RA patients, with an increased risk of myocardial infarction and stroke [43-45].

Diagnostic Criteria

The diagnosis of RA is based on a combination of clinical, laboratory, and imaging findings. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have developed classification criteria to aid in the diagnosis of RA. These criteria include the presence of synovitis in at least one joint, the duration of symptoms (more than six weeks), and the presence of serological markers (RF and ACPA) and acute-phase reactants (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) .Imaging studies, such as X-rays, ultrasound, and magnetic resonance imaging (MRI), are used to assess joint damage and inflammation. X-rays may reveal joint space narrowing, erosions, and osteopenia in affected joints. Ultrasound and MRI are more sensitive in detecting early synovitis and bone erosion, making them valuable tools in the early diagnosis and monitoring of RA [46].

Conventional Disease-Modifying Antirheumatic Drugs (cDMARDs)

Conventional DMARDs have been the cornerstone of RA treatment for many years, aimed at reducing inflammation and preventing joint damage. Methotrexate (MTX) is considered the first-line therapy due to its efficacy and relatively favorable safety profile compared to other cDMARDs.

1. **Methotrexate (MTX):** Methotrexate inhibits dihydrofolatereductase, thereby disrupting folate metabolism and inhibiting purine and pyrimidine synthesis. It also has anti-inflammatory effects by suppressing cytokine production and modulating immune responses [47]. MTX is typically used as monotherapy or in combination with other DMARDs, demonstrating significant efficacy in reducing disease activity and radiographic progression in RA patients [48].
2. **Sulfasalazine:** Sulfasalazine is an oral DMARD that exerts its anti-inflammatory effects by inhibiting NF-κB activation and reducing pro-inflammatory cytokine production [49]. It is commonly used in combination therapy and has shown efficacy in improving symptoms and functional outcomes in RA patients [50].
3. **Hydroxychloroquine:**Hydroxychloroquine is an antimalarial agent with immunomodulatory properties that inhibit Toll-like receptor signaling and interfere with antigen presentation [5]. It is often prescribed for mild RA and in combination with other DMARDs, although its efficacy as a monotherapy in RA is limited [51].

Biologic Disease-Modifying Antirheumatic Drugs (bDMARDs)

Biologic DMARDs revolutionized RA treatment by targeting specific components of the immune system involved in the pathogenesis of RA, leading to improved outcomes in patients who do not respond adequately to cDMARDs.

1. **Tumor Necrosis Factor Inhibitors (TNFi):** TNF inhibitors, such as adalimumab, etanercept, infliximab, certolizumabpegol, and golimumab, block the activity of TNF-α, a key pro-inflammatory cytokine in RA pathogenesis. They reduce synovial inflammation, joint damage, and improve clinical symptoms and functional status [52]. TNFi are effective in both MTX-naive and MTX-resistant RA patients, with a rapid onset of action and sustained efficacy [53].

- **Adalimumab:**Adalimumab is a fully human monoclonal antibody that binds specifically to TNF-α, neutralizing its biological activity. It is administered subcutaneously and has demonstrated efficacy in improving clinical outcomes and inhibiting radiographic progression in RA patients [54].
- **Etanercept:**Etanercept is a fusion protein that acts as a soluble TNF receptor, binding and neutralizing TNF-α. It is administered subcutaneously and has shown efficacy in reducing disease activity and improving quality of life in RA patients [55].
- **Infliximab:** Infliximab is a chimeric monoclonal antibody that binds to TNF-α with high affinity. It is administered intravenously and has been proven effective in achieving clinical remission and inhibiting joint damage in RA patients [56].

2. **Interleukin-6 (IL-6) Inhibitors:** IL-6 inhibitors, such as tocilizumab and sarilumab, target the IL-6 signaling pathway, which plays a crucial role in the inflammatory cascade of RA.

- **Tocilizumab:**Tocilizumab is a humanized monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors, inhibiting IL-6-mediated signaling. It is administered intravenously or subcutaneously and has demonstrated efficacy in improving disease activity, physical function, and quality of life in RA patients [57].
- **Sarilumab:**Sarilumab is a human monoclonal antibody that selectively binds to the IL-6 receptor, inhibiting IL-6 signaling. It is administered subcutaneously and has shown efficacy as monotherapy or in combination with cDMARDs in reducing disease activity and improving clinical outcomes in RA patients [58].

3. **CD20-directed Cytolytic Antibody:** Rituximab is a chimeric monoclonal antibody that targets CD20-positive B lymphocytes, leading to B cell depletion and modulation of the immune response in RA.

- **Rituximab:** Rituximab is administered intravenously and has shown efficacy in reducing disease activity, improving physical function, and inhibiting joint damage in RA patients who have failed to respond adequately to TNFi or other biologics [59]. It is often used in combination with MTX or other DMARDs.

4. **T Cell Co-stimulation Modulator:**Abatacept is a fusion protein that selectively modulates T cell activation by binding to CD80/CD86 on antigen-presenting cells, thereby inhibiting T cell co-stimulation and downstream inflammatory responses in RA.

- **Abatacept:**Abatacept is administered intravenously or subcutaneously and has demonstrated efficacy in reducing disease activity, improving physical function, and inhibiting structural damage in RA patients, particularly in those with early disease or inadequate response to other therapies [60].

Janus Kinase (JAK) Inhibitors

JAK inhibitors represent a newer class of targeted therapies that block intracellular signaling pathways involved in inflammation and immune regulation in RA.

1. **Tofacitinib:**Tofacitinib is an oral JAK inhibitor that selectively targets JAK1 and JAK3, inhibiting cytokine signaling pathways associated with RA pathogenesis, including those involving IL-6, IL-23, and interferons [61]. It has demonstrated efficacy as monotherapy or in combination with cDMARDs in reducing disease activity and improving clinical outcomes in RA patients who have not responded adequately to other therapies [62].
2. **Baricitinib:**Baricitinib is an oral JAK1/JAK2 inhibitor that modulates cytokine signaling pathways involved in RA pathogenesis. It is administered orally and has shown efficacy in reducing disease activity and inhibiting joint damage in RA patients, both as monotherapy and in combination with MTX or other DMARDs [63].

Emerging Therapies and Future Directions

1. **Selective IL-23 and IL-17 Inhibitors:** IL-23 and IL-17 inhibitors are being investigated as potential therapies for RA, targeting specific cytokines implicated in inflammatory responses and joint destruction [64]. Clinical trials are ongoing to evaluate their safety and efficacy in RA patients who do not respond to conventional or biologic DMARDs.
2. **Targeting Other Pathways:** Research continues to explore novel targets and pathways involved in RA pathogenesis, including regulatory T cells, innate immune responses, and epigenetic modifications [66-68]. These efforts aim to

identify new therapeutic targets and develop more personalized treatment strategies for RA patients.

CONCLUSION

The pathogenesis of RA involves a complex interplay of genetic, environmental, and immunological factors that lead to chronic inflammation and joint destruction. Genetic predisposition, particularly involving HLA-DRB1 and other susceptibility genes, and environmental triggers such as smoking and infections, set the stage for the disease. The dysregulated immune response, characterized by the activation of innate and adaptive immune cells, drives the chronic inflammation seen in RA. Key cytokines such as TNF-α, IL-1, and IL-6, along with intracellular signaling pathways like NF-κB, JAK-STAT, and MAPK, mediate the inflammatory response and joint destruction. Effector cells, including synovial fibroblasts, osteoclasts, and chondrocytes, play crucial roles in the pathological mechanisms of RA. Understanding these mechanisms has led to the development of targeted therapies that have significantly improved the management of RA.This comprehensive overview covers the evolution of pharmacologic therapies for rheumatoid arthritis, highlighting the transition from traditional DMARDs to biologic agents and the emergence of JAK inhibitors.

REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58(1):15-25.
2. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987;30(11):1205-1213.
3. Weyand CM, Goronzy JJ. MHC molecules and rheumatoid arthritis. Springer SeminImmunopathol. 1998;20(1-2):25-38.
4. Raychaudhuri S, Sandor C, Stahl EA, et al. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet. 2012;44(3):291-296.
5. Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014;506(7488):376-381.
6. Gregersen PK. Pathways to gene identification in rheumatoid arthritis: PTPN22 and beyond. Immunol Rev. 2020;294(1):1-13.
7. Remmers EF, Plenge RM, Lee AT, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med. 2007;357(10):977-986.
8. Plenge RM, Seielstad M, Padyukov L, et al. TRAF1-C5 as a risk locus for rheumatoid arthritis--a genomewide study. N Engl J Med. 2007;357(12):1199-1209.
9. Suzuki A, Yamada R, Chang X, et al. Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylargininedeiminase 4, are associated with rheumatoid arthritis. Nat Genet. 2003;34(4):395-402.
10. Stolt P, Bengtsson C, Nordmark B, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population-based case-control study, using incident cases. Arthritis Rheum. 2003;48(3):743-750.
11. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006;54(1):38-46.
12. vanVenrooij WJ, van Beers JJ, Pruijn GJ. Anti-CCP antibodies: the past, the present and the future. Nat Rev Rheumatol. 2011;7(7):391-398.
13. Mikuls TR, Payne JB, Yu F, et al. Periodontitis and porphyromonasgingivalis in patients with rheumatoid arthritis. Arthritis Rheum. 2014;66(5):1090-1100.
14. Pender MP, Burrows SR. Epstein-Barr virus and autoimmune diseases. CurrOpinImmunol. 2018;55:83-89.
15. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol. 1996;14:397-440.
16. Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, et al. NETs are a source of citrullinatedautoantigens and stimulate inflammatory responses in rheumatoid arthritis. SciTransl Med. 2013;5(178):178ra40.
17. Guo Q, Wang Y, Xu D, et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018;6:15.
18. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol. 2007;7(6):429-442.
19. Korn T, Bettelli E, Oukka M, et al. IL-17 and Th17 cells. Annu Rev Immunol. 2009;27:485-517.
20. Edwards JC, Cambridge G. B-cell targeting in rheumatoid arthritis and other autoimmune diseases. Nat Rev Immunol. 2006;6(5):394-403.
21. Humby F, Bombardieri M, Manzo A, et al. Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium. PLoS Med. 2009;6(1).
22. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-2219.
23. Kontoyiannis D, Boulougouris G, Manoloukos S, et al. Soluble TNF mediates the transition from pulmonary inflammation to fibrosis. PLoS One. 2008;3(7).
24. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet. 1999;354(9194):1932-1939.
25. Arend WP, Dayer JM. Cytokines and cytokine inhibitors or antagonists in rheumatoid arthritis. Arthritis Rheum. 1990;33(3):305-315.
26. Gabay C, Smith MF, Eidlen D, et al. Interleukin 1 receptor antagonist (IL-1Ra) is an acute-phase protein. J Clin Invest. 1997;99(12):2930-2940.
27. Hirano T. IL-6 in inflammation, autoimmunity and cancer. IntImmunol. 2021;33(3):127-148.
28. Naka T, Nishimoto N, Kishimoto T. The paradigm of IL-6: from basic science to medicine. Arthritis Res. 2002;4Suppl 3.
29. Tak PP, Firestein GS. NF-kappaB: a key role in inflammatory diseases. J Clin Invest. 2001;107(1):7-11.
30. Liu J, Cao X. Cellular and molecular regulation of innate inflammatory responses. Cell MolImmunol. 2016;13(6):711-721.

31. O'Shea JJ, Kontzias A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis. 2013;72Suppl 2.
32. McInnes IB, Taylor PC. Emerging therapies for rheumatoid arthritis. Lancet. 2010;375(9722):2205-2215.
33. Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science. 2002;298(5600):1911-1912.
34. Hammaker D, Firestein GS. "Go upstream, young man": lessons learned from the p38 saga. Ann Rheum Dis. 2010;69Suppl 1.
35. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. Immunol Rev. 2010;233(1):233-255.
36. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005;4(3):130-136.
37. Symmons DP. Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. Best Pract Res ClinRheumatol. 2002;16(5):707-722.
38. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res. 2002;4Suppl 3.
39. MacGregor AJ, Snieder H, Rigby AS, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum. 2000;43(1):30-37.
40. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003;423(6937):356-361.
41. Deane KD, Demoruelle MK, Kelmenson LB, et al. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res ClinRheumatol. 2017;31(1):3-18.
42. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-1108.
43. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016;68(1):1-25.
44. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-977.
45. van der Heijde D, van der Helm-van Mil AHM, Aletaha D, et al. EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria. Ann Rheum Dis. 2013;72(4):479-481.
46. Tanaka Y. Recent progress and perspective in JAK inhibitors for rheumatoid arthritis: from bench to bedside. J Biochem. 2021;169(2):183-191.
47. vanVollenhoven RF. Treatment of rheumatoid arthritis: state of the art 2009. Nat Rev Rheumatol. 2009;5(10):531-541.
48. Smolen JS, Aletaha D, Koeller M, et al. New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370(9602):1861-1874.
49. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. Lancet. 2009;373(9664):659-672.
50. Bykerk VP, Akhavan P, Hazlewood GS, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012;39(8):1559-1582.
51. Verstappen SM, Symmons DP. What is the evidence for the effectiveness of exercise therapy in patients with rheumatoid arthritis? Arthritis Res Ther. 2010;12(2):203.
52. Dougados M, Soubrier M, Antunez A, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis. 2014;73(1):62-68.
53. Akhavan P, Su J, Shen H, et al. What can we learn from clinical trials of preclinical rheumatoid arthritis? Rheumatology (Oxford). 2021;60(3):907-918.
54. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685-699.
55. Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. ClinTher. 2011;33(6):679-707.
56. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet. 2017;389(10086):2338-2348.
57. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with etanercept improves health-related quality of life: results of a randomized controlled trial. J Rheumatol. 1999;26(4):879-884.
58. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. Arthritis Rheum. 2004;50(5):1400-1411.
59. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002;46(6):1443-1450.
60. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372(9636):375-382.
61. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-997.
62. Burmester GR, Feist E, Kellner H, et al. Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). Ann Rheum Dis. 2011;70(5):755-759.
63. Edwards JC, Szczepański L, Szechiński J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572-2581.
64. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353(11):1114-1123.
65. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels

of CP-690,550 versus placebo. Arthritis Rheum. 2009;60(7):1895-1905.
66. vanVollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-519.
67. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76(1):88-95.
68. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med. 2015;373(14):1329-1339.