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Comprehensive Review Of Rheumatoid Arthritis: Insights, Challenges, And Prospects

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Abstract:

This comprehensive review explores the multifaceted landscape of rheumatoid arthritis (RA), encompassing its epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment approaches, and the impact on patients' quality of life. The review delves into the global prevalence of RA, demographic patterns, and associated risk factors, shedding light on the complex interplay of genetics, immunology, and environmental triggers in disease development. The pathophysiological mechanisms involving immunological dysregulation, genetic factors, and environmental triggers are elucidated, providing a foundation for understanding the intricate processes driving RA. Detailed insights into the clinical manifestations of RA, including joint involvement, extra-articular manifestations, and the progression of the disease, are provided. The diagnostic landscape is explored, covering the ACR/EULAR classification criteria, diagnostic imaging, and laboratory tests that facilitate accurate and timely identification of RA. Treatment approaches, from pharmacological therapies like DMARDs and biologics to non-pharmacological interventions such as physical and occupational therapy, emphasizing a holistic management strategy. The economic burden of RA, its impact on healthcare utilization, and the broader societal implications are scrutinized, providing valuable insights into the challenges faced by both individuals and healthcare systems. Prevention and disease management strategies are highlighted, emphasizing the importance of early intervention, patient education, and public health initiatives in mitigating the impact of RA. Current challenges in RA management are outlined, with proposed future research directions aimed at advancing understanding and treatment.

Keywords: Rheumatoid arthritis, DMARDs, Pathophysiology, EULAR classification

Introduction

Rheumatoid arthritis (RA) is a debilitating autoimmune disorder characterized by chronic inflammation of the synovial joints, leading to pain, swelling, and joint deformities with stiffness, it can also damage both joints and extra-articular organs, including the heart, kidney, lung, digestive system, eye, skin and nervous system

[1]. RA predominantly damages the synovial joint capsule and can lead to economic difficulties, early mortality, and persistent impairment. It affects approximately 1% of the global population, with a higher prevalence in women, and poses a significant burden on healthcare systems worldwide. The etiology of RA is multifactorial, involving a complex interplay of genetic predisposition, environmental triggers, and dysregulation of the immune system [2]. Several forms of arthritis have been studied and characterised in order to categorise them into two groups: non-inflammatory arthritis (osteoarthritis) and inflammatory arthritis that are brought on by bacterial and viral infections (Staphylococcus aureus, Neisseria gonorrhoea, basic calcium phosphate disease, gout), autoimmune processes, or crystallographic deposition [3]. Unlike osteoarthritis, which primarily results from mechanical wear and tear, RA is driven by an immune-mediated attack on the synovium, the lining of the joint capsule. This persistent inflammation can lead to the destruction of cartilage and bone within the joint, causing irreversible damage if not effectively managed.

Early diagnosis and intervention are crucial in managing RA and preventing long-term disability. The classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) play a pivotal role in identifying individuals with RA [4,5]. Advances in diagnostic imaging, blood testing and biomarker testing have further enhanced our ability to diagnose RA accurately. Over the past decades, significant strides have been made in the treatment of RA. Disease-modifying antirheumatic drugs (DMARDs), including biologics and more recently, Janus kinase (JAK) inhibitors, have revolutionized RA management, aiming not only to alleviate symptoms but also to modify the underlying disease process. Non-pharmacological interventions, such as physical therapy and lifestyle modifications, complement pharmacotherapy in providing holistic care to individuals with RA [6]. Although RA has no known cure, the goal of the treatment plan is to identify the condition as soon as possible and get it to a low disease activity state (LDAS). A variety of combinations of systems are available for quantifying disease activity, including the Clinical Disease Assessment Index (CDAI), Simplified Disease Activity Assessment Index (SDAI), and Disease Activity Score employing 28 joints (DAS-28) [7]. Non-steroidal anti-inflammatory medications (NSAIDs) and corticosteroids, when used universally in pharmacologic treatment, have been shown to be useful in reducing pain and stiffness but not in slowing the course of the illness.

Despite these therapeutic advances, challenges persist in achieving optimal outcomes for all RA patients. This review explores the current understanding of RA, encompassing epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment strategies. Furthermore, it highlights emerging research areas, discusses challenges in disease management, and suggests potential future directions for improving the overall care and quality of life for individuals living with RA.

Epidemiology of RA

Rheumatoid arthritis (RA) is a widespread autoimmune disease with a global impact on public health, affecting individuals across diverse demographic and geographic settings. Globally, the incidence of RA varies, although it is often greater in industrialised nations. This difference in frequency can be attributed to a variety of variables, including genetics, insufficient reporting in some regions of the world, and susceptibility to environmental risk factors. RA exhibits variability in prevalence across different regions and populations. Globally, it is estimated that approximately 0.5-1% of the adult population is affected by RA, making it one of the most common autoimmune inflammatory arthritis conditions [8]. Both modifiable lifestyle-related variables and unmodifiable characteristics, such genetics and sex, are common risk factors for RA. The proportion of female to male RA cases is 3:1, meaning that women are more likely than males to have the disease. Furthermore, smoking, being overweight, and being among pollutants are risk factors. The etiology of RA is multifactorial, involving a complex interplay of genetic, environmental, and hormonal factors. Several identified risk factors contribute to the development of RA like genetic predisposition, environmental triggers, hormonal factors and age etc. Genetic predisposition means the individuals with a family history of RA are at an increased risk of developing the condition. Specific genetic markers, such as certain human leukocyte antigen (HLA) alleles, have been associated with a higher susceptibility to RA. Seropositive and seronegative rheumatoid arthritis (RA) can be distinguished from one another by the presence or absence of rheumatoid factor (RF) and ACPAs. The risk factors that are implicated can also vary. The major genetic factors linked to an ACPA-positive subtype are tyrosine phosphatase non-receptor type 22 (PTPN22) risk alleles, human leukocyte antigen D-related (HLA-DR) alleles, and genes related to tumour necrosis factor-receptor associated factor 1 and complement component 5 (TRAF1/C5), whereas interferon regulatory factor 5 (IRF-5) is limited to the ACPA-negative subtype [9,10]. Hormonal influences, particularly in women, play a role in the development of RA. The increased prevalence of RA in women during their reproductive years and changes in disease activity during pregnancy and menopause suggest a hormonal component in the pathogenesis of RA.

While RA can occur at any age, it most commonly manifests in middle adulthood. The risk increases with age, with the highest incidence observed in individuals over the age of 60 [11].

Pathophysiology of RA

Several theories have been proposed, despite the fact that the pathophysiological processes underlying RA remain unclear. Immunoglobulin G (IgG), vimentin and type 2 collagen are examples of altered self-antigens that result from an interaction between environmental variables and epigenetic changes on the genomic structure. Citrullination is a post-translational alteration of these proteins containing arginine residues that can be achieved by peptidyl arginine deiminases [12,13]. Additionally, cytokine production from joint diseases such as synovial hyperplasia or synovial infections can result in joint inflammation and modified self-antigens. The pathophysiology of RA involves intricate interactions between immunological, genetic, and environmental factors, contributing to the dysregulation of the immune system and the subsequent inflammatory cascade. Genetic susceptibility is a significant component of RA pathophysiology, as evidenced by the increased risk in individuals with a family history of the disease. Certain genetic markers, particularly human leukocyte antigen (HLA) alleles such as HLA-DRB1, are strongly associated with RA. The presence of specific shared epitope (SE) sequences within HLA-DRB1 confers an elevated risk, and the interaction between genetic predisposition and environmental factors further contributes to disease development. Moreover, non-HLA genes, such as PTPN22, STAT4, and CTLA4, have been implicated in RA susceptibility. These genes influence various aspects of the immune response, including T-cell activation, cytokine signaling, and immune regulation. The interplay between these genetic factors contributes to the complexity and heterogeneity of RA pathogenesis [14].

The significant feature of RA is the aberrant activation of the immune system, specifically the involvement of T lymphocytes, B lymphocytes, and synovial macrophages. The process begins with the activation of CD4+ T-helper cells, which release pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines orchestrate a cascade of events, including the recruitment of immune cells to the synovium and the stimulation of synovial fibroblasts to produce matrix metalloproteinases (MMPs), enzymes that contribute to the degradation of cartilage and bone [15]. B lymphocytes play a crucial role in RA pathogenesis by producing autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs). These autoantibodies form immune complexes that deposit in the joints, contributing to local inflammation and the activation of the complement system. The resulting chronic synovial inflammation leads to pannus formation, an invasive tissue that erodes cartilage and bone within the joint [16].

Environmental factors play a role in triggering and exacerbating RA in genetically susceptible individuals. Smoking is one of the most well-established environmental risk factors for RA, contributing to citrullination of proteins and the production of ACPAs. Additionally, microbial infections, particularly those affecting the respiratory and gastrointestinal tracts, have been implicated in RA pathogenesis [17]. Molecular mimicry and the activation of the immune response by infectious agents may contribute to the initiation and perpetuation of the autoimmune response in RA. Exposure to silica dust and other occupational pollutants is associated with an increased risk of RA, suggesting a potential link between environmental exposures and the development of autoimmunity. Understanding the interactions between genetics and environmental factors is essential for unraveling the triggers of RA and developing targeted preventive strategies [18].

Clinical Manifestation

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that primarily affects the joints, leading to a spectrum of clinical manifestations. The disease's course is characterized by joint inflammation, pain, and stiffness, with potential involvement of multiple organ systems. Understanding the clinical manifestations is crucial for early diagnosis and the implementation of effective management strategies.

Joint involvement

The main feature of RA is synovitis, inflammation of the synovial membrane lining the joints. This inflammation typically affects joints on both sides of the body, often in a symmetrical pattern. The small joints of the hands and feet are frequently involved, but larger joints such as the knees, shoulders, and hips can also be affected. The inflamed synovium leads to joint swelling, warmth, and tenderness, causing pain and limiting range of motion. Morning stiffness is a characteristic symptom, often lasting for more than 30 minutes, and can be a key indicator of RA [19,20]. Over time, chronic synovial inflammation may result in joint damage, leading to deformities and functional impairment. This destructive process can be observed through imaging techniques

such as X-rays and magnetic resonance imaging (MRI), revealing erosions, joint space narrowing, and periarticular osteopenia [21].

Extra-articular manifestations

While RA primarily affects the joints, it can also manifest in various extra-articular organs and systems, contributing to the systemic nature of the disease. Extra-articular manifestations can involve: Rheumatoid nodules, cardiovascular involvement, pulmonary manifestations, ocular involvement, hematologic abnormalities, neurological complications etc. Rheumatoid nodules are subcutaneous nodules that commonly form over bony prominences or in areas of repeated pressure. While they are typically painless, nodules can cause discomfort and may be indicative of more aggressive disease. RA is associated with an increased risk of cardiovascular disease, including atherosclerosis and myocardial infarction. Due to the pathological processes involving multiple cardiac structures, RA patients may have an increased risk of cardiovascular mortality. These conditions include atherosclerosis, arterial stiffness, coronary arteritis, congestive heart failure, valvular disease, and fibrinous pericarditis [22]. It could have prognostic indicators for conditions like dyslipidemia and hypertension. Pleural effusions, pulmonary fibrosis, interstitial lung disease, and arteritis are common, asymptomatic pulmonary consequences. Smokers are more likely to experience potentially fatal complications from RA [2]. RA can affect the eyes, causing conditions like scleritis and keratitis. Dry eye syndrome is also common in individuals with RA. Although neurological problems can lead to peripheral neuropathy and cervical myelopathy, renal symptoms such as glomerulonephritis and interstitial renal disease are uncommon and are associated with vasculitis. Due to hepcidin activation, which prevents iron transfer, anaemia is the most prevalent hematologic deviation in people with RA. Additionally, hepcidin has been shown to be a useful predictive biomarker in RA. Cancers, neutropenia, eosinophilia, and thrombocytopenia are other EAMs [23].

Disease Progression

RA is characterized by a variable and often unpredictable disease course. The progression of RA can be categorized into different phases: early inflammatory phase, established disease phase and remission and flares. Early inflammation phase is characterized by synovitis, joint swelling, and pain. Early intervention during this phase is crucial to prevent irreversible joint damage. Chronic inflammation persists, leading to joint damage and potential deformities. Disease-modifying antirheumatic drugs (DMARDs) are often employed to slow or halt disease progression. RA may exhibit periods of remission, where symptoms are minimal, and flares, characterized by increased disease activity. The goal of treatment is to achieve and maintain remission while managing flares effectively [24].

Diagnosis and classification criteria

The assessment of clinical features, such as symptoms and indicators, predictive laboratory biomarkers, differential diagnosis, complications, extra-articular manifestations, etc., is crucial to the therapy of RA. It is crucial to diagnose RA as soon as possible in order to distinguish between different forms of autoimmune diseases and kinds of arthritis, to start the right therapy right away, and to avoid long-term complications.

ACR/EULAR classification criteria

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) collaborated to establish classification criteria for RA in 2010, providing a standardized framework for identifying individuals with the disease. The criteria encompass joint involvement, serology (including RF or ACPA), acute-phase reactants (CRP or ESR), and symptom duration. A scoring system aids in stratifying patients into different likelihood categories, facilitating early diagnosis and initiation of appropriate treatment. Patients are classified as having RA if their score is ≥6. There are two requirements that must be fulfilled in order to be qualified for a new round of testing. The initial need is the presence of synovitis, as determined by a specialist, with edoema in at least one joint, excluding the joints that are commonly affected by osteoarthritis, namely the distal interphalangeal joint, the first metatarsophalangeal joint, and the first carpometacarpal joint. The patient's absence of a conflicting synovitis diagnosis is the second prerequisite for using the criterion. Additionally, the ankles, hips, elbows, shoulders, and knees are included in the big joint group, whereas the wrists, second through fifth metatarsophalangeal joints, and proximal interphalangeal joints comprise the small joint category. The ACR/EULAR classification criteria for RA evaluation is listed below in fig.1 [25].

2010 ACR/EULAR CRITERIA FOR RA DIAGNOSIS		
Add score of categories A-D, score of ≥ 6/10 needed to classify patient as having definite RA		
A	**Joint involvement**	**Score**
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (≥1 small joint)	5
B	**Serology (≥1 test result needed)**	
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
C	**Acute-phase reactants (≥1 test result needed)**	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D	**Duration of symptoms**	
	< 6 weeks	0
	≥ 6 weeks	1

Figure 1: The 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA evaluation [25].

Diagnostic, Prognostic and Predictive Biomarkers in RA

The exploration and refinement of biomarker panels are promising advancements in medical diagnostics, offering roles in diagnosis, prognosis, prediction, and therapy. In the past, the ACR 1987 criteria relied solely on RF as a biomarker, but the latest classification integrates four biomarkers (RF, ACPA, ESR, CRP), each with certain limitations. Recent studies have identified additional diagnostic proteins for early RA diagnosis, including antibodies against mutated citrullinated vimentin (anti-MCV), antibodies against carbamylated proteins (anti-CarP), and 14-3-3 eta protein. A systematic review found no significant difference between cyclic ACPA and anti-MCV, suggesting the latter as a diagnostic tool when RA and ACPA are negative. Anti-CarP, detected in RA patient serum, is associated with pre-symptomatic phases and holds prognostic potential [26]. Recent investigations demonstrate the importance of gene profiles as diagnostic tools. Comparisons of FLS from healthy individuals to FLS-RA reveal significant differences in gene expression, including heat-shock protein family A members, matrix metalloproteinase 1 (MMP1), matrix metalloproteinase 13 (MMP13), and tumor necrosis factor ligand superfamily member 10 (TNFSF10) genes. Proteomics advancements allow the identification of diagnostic protein panels, with serum amyloid A-4 protein (SAA4), angiotensinogen (AGT), retinol-binding protein-4 (RBP4), and vitamin D-binding protein (VDBP) showing accuracy for seronegative RA patients. Glycoprotein YKL-40 also emerges as a promising diagnostic biomarker [27]. Certain biomarkers (anti-MCV, RF, 14-3-3 eta protein, ACPA) extend beyond diagnosis to serve as prognostic tools linked to severe phases of RA. Further research is needed to identify new potential prognostic biomarkers. Predictive biomarkers are crucial for therapeutic management, and studies indicate that anti-CCP, anti-MCV, 14-3-3 eta, cartilage oligomeric matrix protein (COMP), survivin, and calprotectin are correlated with a good predictability of treatment response [28].

Imaging Diagnosis of RA

Accurate diagnosis in rheumatoid arthritis (RA) involves associating biomarker detection and quantification with advanced imaging tools. The ACR-EULAR 2010 classification incorporates ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) for early diagnosis due to their superior accuracy compared to conventional radiographs. While X-rays are still employed for late-stage changes due to availability and cost, they have limitations such as radiation exposure, low sensitivity in detecting early erosions, and 2D representation of 3D structures [29]. Radiographic hallmarks of RA include symmetrical abnormalities, periarticular osteopenia, joint space narrowing, marginal degradation, soft tissue swelling, synovial cysts, and nodules. Ultrasonography excels in detecting small erosions and differentiating active from inactive inflammatory tissues using Doppler ultrasound. CT, though rarely used due to ionizing radiation, finds applications in 3D imaging. MRI, considered the most accurate imaging tool, can distinguish joint effusion from synovitis, detect early erosions, hypertrophies, and serves as the gold standard for bone marrow edema detection. However, a longitudinal study found no correlation between MRI-detected changes and RA

progression in symptomatic patients. The choice of imaging tools depends on the stage of RA progression. MRI is ideal for early changes, except for joint space widening where CT is preferable. For late changes, all mentioned imaging tools yield positive results. Future challenges and optimization strategies in medical imaging include thermography, near-infrared imaging (NIR), positron emission tomography (PET), and single-photon emission computerized tomography (SPECT) [30]. These advancements hold promise for refining diagnostic capabilities and optimizing the management of rheumatoid arthritis.

Treatment Approaches for RA

Effectively managing rheumatoid arthritis (RA) involves a multidimensional approach that combines pharmacological and non-pharmacological interventions. This explores various treatment modalities, encompassing pharmacological therapies such as Disease-Modifying Antirheumatic Drugs (DMARDs), Biologic DMARDs, Janus Kinase (JAK) Inhibitors, as well as non-pharmacological interventions like physical therapy, occupational therapy, and lifestyle modifications.

Table 1. Modern pharmacologic therapies for rheumatoid arthritis

Classification	Drug name	Mechanism of action	Potential mechanisms/side effects	References
Anti-Nonsteroidal Inflammatory Drugs (NSAIDs)	Ibuprofen, Naproxen	Inhibition of COX-1 and COX-2 enzymes, reducing inflammation and pain	Gastrointestinal bleeding, renal dysfunction, cardiovascular risks	31
Disease-modifying Antirheumatic Drugs (DMARDs)	Methotrexate	Inhibits dihydrofolate reductase, suppressing immune response	Hepatic toxicity, bone marrow suppression, gastrointestinal issues	32
DMARDs (Biological)	Adalimumab (TNF inhibitor)	Targets tumor necrosis factor (TNF), reducing inflammation	Increased risk of infections, injection site reactions, autoimmune reactions	33
DMARDs (Biological)	Rituximab (B-cell depleting)	Targets B-cells, reducing immune response	Infusion reactions, increased susceptibility to infections, cardiovascular risks	34
DMARDs (Biological)	Tocilizumab (IL-6 inhibitor)	Blocks interleukin-6 (IL-6), reducing inflammation	Increased risk of infections, liver enzyme abnormalities, gastrointestinal perforations	35
Janus Kinase (JAK) Inhibitors	Tofacitinib	Inhibits JAK enzymes, reducing inflammation	Increased risk of infections, liver enzyme abnormalities, cardiovascular risks	36
Tumor Necrosis Factor (TNF) Inhibitors	Etanercept	Binds to TNF, inhibiting its activity	Injection site reactions, increased risk of infections, autoimmune reactions	33
Interleukin-1 (IL-1) Inhibitor	Anakinra	Blocks IL-1, reducing inflammation	Injection site reactions, increased risk of infections, hypersensitivity reactions	37
Interleukin-17 (IL-17) Inhibitors	Secukinumab, Ixekizumab	Blocks IL-17, reducing inflammation	Upper respiratory tract infections, injection site reactions, gastrointestinal issues	38

New Perspectives and future directions in the treatment of RA

In recent decades, significant strides have been made in the management of rheumatoid arthritis (RA), resulting in improved patient outcomes. This progress is attributed to the identification of various pathways involved in RA pathogenesis. Despite these advancements, challenges persist, prompting ongoing research for a more comprehensive understanding and enhanced therapeutic strategies. Key unmet needs in RA management

include deciphering the comparable efficacies of diverse therapies, understanding factors contributing to reduced responsiveness in certain patients over time, early detection and aggressive treatment of pre-RA stages, and improving the efficacy and safety profiles of novel compounds, particularly Janus Kinase inhibitors (JAKis) [39]. Current research endeavors aim to address these challenges. Experimental models explore novel therapeutic targets, with potential agents at various testing stages targeting complete RA remission. Recent studies investigate small molecular metabolite targets (prostaglandins, thromboxane A2, leukotriene B4 receptor), epigenetic targets (DNA methylation, RNA methylation, histone modification), and other protein targets (p38 mitogen-activated protein kinase, G protein-coupled receptor kinase 2, granulocyte-macrophage colony-stimulating factor) [40]. Notably, mesenchymal stem cells (MSCs) emerge as a promising therapeutic avenue, demonstrating the potential to differentiate into tissues like bone and cartilage, coupled with immunosuppressive properties. Clinical trials and animal studies suggest that MSC treatment reduces proinflammatory responses and improves RA symptoms. Confirmation of Toll-like receptor 4's role in RA pathogenesis makes it a target for therapeutic compounds. Compounds targeting this receptor or its ligands, such as heat-shock protein crystalline or tenascin C, hold promise for optimization. Therapeutic options for RA continue to diversify, with ongoing studies expected to make significant contributions. The exploration of new molecular targets, therapeutic agents, and strategies to mitigate side effects presents opportunities for transformative advancements. A personalized approach, integrating genetic studies with evidence-based medicine, emerges as a promising avenue to revolutionize the future of RA treatment and potentially achieve cures [41].

Conclusion

In conclusion, this comprehensive review delves into the multifaceted landscape of rheumatoid arthritis (RA), spanning its epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment approaches, and the broader impact on patients' lives. The exploration of global prevalence, demographic patterns, and risk factors provides a foundational understanding of RA's reach. Insights into the immunological basis, genetic factors, and environmental triggers shed light on the complex mechanisms driving the disease. The examination of clinical manifestations, diagnosis criteria, and classification methods equips clinicians with tools for accurate identification. Treatment approaches, both pharmacological and non-pharmacological, offer a holistic perspective on managing RA, addressing disease modification and enhancing patients' overall well-being. The review extends to emerging therapies, research advances, and the evolving landscape of personalized medicine, demonstrating the continuous efforts to refine RA management. Quality of life considerations and patient perspectives highlight the broader impact of RA beyond physical symptoms, emphasizing the importance of support and education. Comorbidities, health economics, and societal burdens further underscore the multifaceted nature of RA, necessitating a comprehensive approach to address its complexities. Prevention and disease management strategies, including early intervention, patient education, and public health initiatives, showcase proactive measures to mitigate the impact of RA.

References

1. Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F, Giacomelli R, Cipriani P. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. Autoimmunity reviews. 2021;20(2):102735.
2. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular manifestations in rheumatoid arthritis. Maedica. 2010;5(4):286.
3. Joseph A, Brasington R, Kahl L, Ranganathan P, Cheng TP, Atkinson J. Immunologic rheumatic disorders. Journal of Allergy and Clinical Immunology. 2010;125(2):S204-15.
4. Cho SK, Kim D, Won S, Lee J, Choi CB, Choe JY, Hong SJ, Jun JB, Kim TH, Koh E, Lee HS. Factors associated with time to diagnosis from symptom onset in patients with early rheumatoid arthritis. The Korean journal of internal medicine. 2019;34(4):910.
5. Initiative C. 2010 rheumatoid arthritis classification criteria. Arthritis & Rheumatism. 2010;62(9):2569-81.
6. Initiative C. 2010 rheumatoid arthritis classification criteria. Arthritis & Rheumatism. 2010 Sep;62(9):2569-81.
7. Ometto F, Botsios C, Raffeiner B, Sfriso P, Bernardi L, Todesco S, Doria A, Punzi L. Methods used to assess remission and low disease activity in rheumatoid arthritis. Autoimmunity reviews. 2010;9(3):161-4.
8. Smith E, Hoy DG, Cross M, Vos T, Naghavi M, Buchbinder R, Woolf AD, March L. The global burden of other musculoskeletal disorders: estimates from the Global Burden of Disease 2010 study. Annals of the rheumatic diseases. 2014;73(8):1462-9.

9. Mankia K, Siddle HJ, Kerschbaumer A, Rodriguez DA, Catrina AI, Cañete JD, Cope AP, Daien CI, Deane KD, El Gabalawy H, Finckh A. EULAR points to consider for conducting clinical trials and observational studies in individuals at risk of rheumatoid arthritis. Annals of the Rheumatic Diseases. 2021;80(10):1286-98.
10. Zhang X, Li W, Zhang X, Zhang X, Jiang L, Guo Y, Wang X. Association between polymorphism in TRAF1/C5 gene and risk of rheumatoid arthritis: a meta-analysis. Molecular biology reports. 2014;41:317-24.
11. Finckh A, Gilbert B, Hodkinson B, Bae SC, Thomas R, Deane KD, Alpizar-Rodriguez D, Lauper K. Global epidemiology of rheumatoid arthritis. Nature Reviews Rheumatology. 2022;18(10):591-602.
12. Curran AM, Naik P, Giles JT, Darrah E. PAD enzymes in rheumatoid arthritis: pathogenic effectors and autoimmune targets. Nature Reviews Rheumatology. 2020;16(6):301-15.
13. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. Journal of autoimmunity. 2020;110:102400.
14. Damerau A, Gaber T. Modeling rheumatoid arthritis in vitro: From experimental feasibility to physiological proximity. International journal of molecular sciences. 2020;21(21):7916.
15. Van Drongelen V, Holoshitz J. Human leukocyte antigen–disease associations in rheumatoid arthritis. Rheumatic Disease Clinics. 2017;43(3):363-76.
16. Bizzaro N, Bartoloni E, Morozzi G, Manganelli S, Riccieri V, Sabatini P, Filippini M, Tampoia M, Afeltra A, Sebastiani G, Alpini C. Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis research & therapy. 2013;15:1-9.
17. Yu HC, Lu MC. The roles of anti-citrullinated protein antibodies in the immunopathogenesis of rheumatoid arthritis. Tzu-Chi Medical Journal. 2019;31(1):5.
18. Alsaber A, Pan J, Al-Herz A, Alkandary DS, Al-Hurban A, Setiya P. Influence of ambient air pollution on rheumatoid arthritis disease activity score index. International journal of environmental research and public health. 2020;17(2):416.
19. Wasserman AM. Diagnosis and management of rheumatoid arthritis. American family physician. 2011;84(11):1245-52.
20. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. Jama. 2018;320(13):1360-72.
21. Salaffi F, Gutierrez M, Carotti M. Ultrasound versus conventional radiography in the assessment of bone erosions in rheumatoid arthritis. Clin Exp Rheumatol. 2014;32(1 Suppl 80):S85-90.
22. Baghdadi LR, Woodman RJ, Shanahan EM, Mangoni AA. The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. PloS one. 2015;10(2):e0117952.
23. Chen Y, Xu W, Yang H, Shao M, Xu S, Deng J, Gao X, Liu H, Shuai Z, Xu S, Pan F. Serum levels of hepcidin in rheumatoid arthritis and its correlation with disease activity and anemia: a meta-analysis. Immunological investigations. 2021;50(2-3):243-58.
24. Haddani F, Guich A, Youssoufi T, Boudhar E, Abouqal R, Achemlal L, Allali F, Bahiri R, Bouchti E, Maghraoui E, Ghozlani I. Comorbidities in rheumatoid arthritis: The RBSMR study. Int. J. Clin. Rheumtol. 2020;15:1-0.
25. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu ET, Tugwell P. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. Cmaj. 2009;181(11):787-96.
26. De Germay S, Bagheri H, Despas F, Rousseau V, Montastruc F. Abatacept in rheumatoid arthritis and the risk of cancer: a world observational post-marketing study. Rheumatology. 2020;59(9):2360-7.
27. Mun S, Lee J, Park M, Shin J, Lim MK, Kang HG. Serum biomarker panel for the diagnosis of rheumatoid arthritis. Arthritis Research & Therapy. 2021;23:1-0.
28. Marotta A, Maksymowych WP. SAT0070 levels of 14-3-3eta predict good eular response to anti-TNF treatment in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2014;73:615.
29. Kgoebane K, Ally MM, Duim-Beytell MC, Suleman FE. The role of imaging in rheumatoid arthritis. SA journal of radiology. 2018;22(1):1-6.
30. Giles JT. Extra-articular manifestations and comorbidity in rheumatoid arthritis: Potential impact of pre–rheumatoid arthritis prevention. Clinical Therapeutics. 2019;41(7):1246-55.
31. Linares V, Alonso V, Domingo JL. Oxidative stress as a mechanism underlying sulfasalazine-induced toxicity. Expert opinion on drug safety. 2011;10(2):253-63.

32. Brown PM, Pratt AG, Isaacs JD. Mechanism of action of methotrexate in rheumatoid arthritis, and the search for biomarkers. Nature Reviews Rheumatology. 2016;12(12):731-42.
33. Kim EY, Moudgil KD. Immunomodulation of autoimmune arthritis by pro-inflammatory cytokines. Cytokine. 2017;98:87-96.
34. Mota P, Reddy V, Isenberg D. Improving B-cell depletion in systemic lupus erythematosus and rheumatoid arthritis. Expert review of clinical immunology. 201734;13(7):667-76.
35. Raimondo MG, Biggioggero M, Crotti C, Becciolini A, Favalli EG. Profile of sarilumab and its potential in the treatment of rheumatoid arthritis. Drug Design, Development and Therapy. 2017:1593-603.
36. Yamaoka K. Janus kinase inhibitors for rheumatoid arthritis. Current opinion in chemical biology. 2016;32:29-33.
37. Cavalli G, Dinarello CA. Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies. Rheumatology. 2015;54(12):2134-44.
38. Kim EK, Kwon JE, Lee SY, Lee EJ, Kim DS, Moon SJ, Lee J, Kwok SK, Park SH, Cho ML. IL-17-mediated mitochondrial dysfunction impairs apoptosis in rheumatoid arthritis synovial fibroblasts through activation of autophagy. Cell Death & Disease. 2018;8(1):e2565.
39. Johnson KJ, Sanchez HN, Schoenbrunner N. Defining response to TNF-inhibitors in rheumatoid arthritis: the negative impact of anti-TNF cycling and the need for a personalized medicine approach to identify primary non-responders. Clinical rheumatology. 2019;38(11):2967-76.
40. Huang J, Fu X, Chen X, Li Z, Huang Y, Liang C. Promising therapeutic targets for treatment of rheumatoid arthritis. Frontiers in immunology. 2021;12:686155.
41. Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020;9(4):880.