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MOLECULAR PATHOGENESIS AND CLINICAL IMPACT OF RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

Mba Ogbonnaya*[1], Obidiegwu Onyeka Chinweuba*[3], Abone Harrison Odera*[4], Chukwuka Benjamin Uzodinma*[1], Oraekei Daniel Ikechukwu[1,2]*

[1]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, PMB 5025 Awka, Anambra State, Nigeria.

[2]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences. Oliva University, Number 4 & 5 Mayugi Avenue, Mukaza, Bujumbura, Burundi.

[3]Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, PMB 5025 Awka, Anambra State, Nigeria.

[4]Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, PMB 5025 Awka, Anambra State, Nigeria.

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***Corresponding Author: Oraekei Daniel Ikechukwu**
Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, PMB 5025 Awka, Anambra State, Nigeria.

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ABSTRACT

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation that is caused by the interaction between genes and environmental factors, such as tobacco, and it involves the synovial joints. This study aims to provide a comprehensive review of the regulatory mechanisms and the pathological significance of rheumatoid arthritis. Some scientific databases, including MDPI, MEDLINE, EMBASE, ScienceDirect, Google Scholar, Web of Science, and Scopus, were searched. The studies considered were original research articles, meta-analyses, randomized controlled trials, and systematic reviews. Articles reviewed gave information about rheumatoid arthritis regulatory mechanisms and pathophysiology, epidemiology, genetics, and environmental triggers, autoantibodies production, signaling pathway, cytokine network, synovial hyperplasia and pennus formation, bone erosion, angiogenesis and hypoxia in rheumatoid arthritis, pathological significance and clinical consequences of rheumatoid arthritis, and treatment targets, prognosis, patient outcome, and future perspectives of rheumatoid arthritis. Rheumatoid arthritis prevalence was 0.5-1.0%, and it affects mostly women. Cascades of immune cells regulate rheumatoid arthritis, and environmental triggers include smoke. Autoantibodies increase the risk of developing rheumatoid arthritis, and the main signaling pathway is the Janus-activated kinase pathway. Other factors and several treatment targets were identified, and surgical intervention could be used. Novel therapeutic targets were found. Despite the fact that many regulatory mechanisms for rheumatoid arthritis have been revealed, and drugs have been designed to target these mechanisms, a radical cure of the ailment has not yet been achieved. A lot of studies are still ongoing with the intention of discovering a lasting solution to this autoimmune problem –rheumatoid arthritis.

KEYWORDS: Autoantibodies, bone erosion, regulatory mechanisms, rheumatoid arthritis, pathophysiology.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation, often caused by interactions between genetic and environmental factors, and involving synovial joints [1]. The diagnosis of RA is based on the presence of symptoms and signs of active joint inflammation, as well as biomarkers such as autoantibodies and imaging findings that can demonstrate joint inflammation and/or damage [2, 3]. It is also characterized by synovial inflammation, joint injury, and deformity in the limbs, and it can cause complications in multiple systems, many of which can seriously affect patients' quality of life and even significantly increase the risk of death [4]. RA has also been described as an autoimmune disease characterized by chronic, erosive polyarthritis, and its main pathological features include synovitis and cartilage destruction, and clinical manifestations are joint pain, swelling, and limitation of movement [5, 6]. RA affects many joints throughout the body, primarily the hands and feet, and may also affect any synovial membrane-lined joint, leading to extra-articular symptoms such as skin, pulmonary, cardiac, ocular, neurological, and hematological manifestations [7]. The ailment can also manifest as severe interstitial lung disease (ILD) [8]. RA can negatively impact quality of life due to its ability to cause chronic pain and physical function limitations [9]. RA manifests clinically as pain, swelling, and morning stiffness in small joints, particularly the proximal interphalangeal, metacarpophalangeal, wrist, and knee joints [10]. It is the most common systemic inflammatory rheumatic disease, and its association with significant burden at the patient and societal level was confirmed [11]. RA is multifactorial and of unknown etiology, primarily affecting the joints, though extra-articular manifestations can occur [12].

Epidemiology of rheumatoid arthritis

RA has a prevalence of 0.5–1.0% according to most epidemiological studies, predominantly affects females (male-to-female ratio of 1:2-1:3), and can manifest at any age, peaking around 60 years [13]. RA prevalence was reported to be higher in urban settings than rural settings [14]. Globally, the age-standardized prevalence (ASPR) and incidence rate (ASIR) of RA increased from 1980 to 2019 [15]. In 2020, an estimated 17.6 million people worldwide had RA, with an age-standardized global prevalence rate of 208·8 cases per 100 000 population, representing a 14·1% increase since 1990; prevalence was higher in females [16]. Over the past 32 years, the global burden of rheumatoid arthritis among the elderly, especially females, has significantly increased, with high Sociodemographic Index (SDI) regions bearing the heaviest burden, while Low and Lower-middle SDI regions are experiencing rapid increases in burden [17]. An earlier study reported that the disease affects women primarily, with a female-to-male ratio of three to one [18]. The global prevalence of RA between 1980 and 2019 was 460 per 100,000 population, with variations across geographical locations and study methodologies [19]. In Korea, the estimated prevalence of RA ranged from 0.27% to 1.85%, and the prevalence of extra-articular manifestations such as interstitial lung disease (ILD) and Sjögren's syndrome (SS) was also reported [20].

METHODS

This study is a narrative review in which scientific databases, including MDPI, Medline, Embase, ScienceDirect, Google Scholar, Web of Science, and Scopus, were searched. The studies considered were original research articles, meta-analyses, randomized controlled trials, and systematic reviews that were published from 2020 to 2026. Articles reviewed gave information about RA regulatory mechanisms and pathophysiology, epidemiology, genetics, and environmental triggers, autoantibodies production, signaling pathway, cytokine network, synovial hyperplasia and pennus formation, bone erosion, angiogenesis and hypoxia in RA, pathological significance and clinical consequences of RA, and treatment targets, prognosis, patient outcome, and future perspectives of RA.

RESULTS

According to the literature, RA prevalence is 0.5-1.0% and affects mostly women. Cascades of immune cells regulate RA. Main genetic risk factors, including human leukocyte antigen (HLA) genes and non-HLA variants, and environmental triggers include cigarette smoke, occupational exposures, air pollution, infections, obesity, chronic stress, and inadequate vitamin D intake. Autoantibodies worsen the risk of developing RA. Main signaling pathways related to RA include: The Janus-activated Kinase (JAK), Signal Transduction and Activator of Transcription (STAT), Notch, Mitogen-Activated Protein Kinase (MAPK), Wingless/Integrated (Wnt), phosphatidylinositol 3 kinase (PI3K), and spleen tyrosine kinase (SYK) signaling pathways. The main signaling pathway was the Janus-activated kinase pathway. Other factors and several treatment targets were identified, and surgical intervention could be used to treat RA. Novel therapeutic targets were found.

DISCUSSION

Regulatory Mechanisms and Pathophysiology

RA is regulated by a self-sustaining cascade of immune cell activation, pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukins (IL-6, IL-17), epigenetic modifications, and other factors that contribute to the development of RA, like osteoclasts, synovial fibroblasts, T cells, and B cells [21]. The complex interplay of those factors results in such pathological abnormalities as synovial hyperplasia, bone injury, and multi-joint inflammation. Three stages of RA progression are reported in another study: a non-specific inflammatory stage, amplified by T-cell activation in the synovium; a chronic inflammatory stage; and a tissue-damage stage, mediated by cytokines such as IL-1, IL-6, and TNF-α [22]. Recent progress in understanding the mechanisms of RA pathogenesis has highlighted the critical roles of epigenetic regulatory processes, including DNA methylation, histone modifications, and microRNA (miRNA) regulation [23]. The pathogenesis of RA involves a complex interplay of genetic predisposition and environmental factors, which together drive the dysregulated activation of both the innate and adaptive immune systems [24]. RA is characterized by its unique immunopathology, which involves infiltration of inflammatory cells into the synovial membrane, leading to destruction of articular structures [25]. Immunological abnormalities, inflammatory pathways, genetic and epigenetic alterations, and metabolic disorders participate in RA pathogenesis [26]. In RA, inflammation and immune reactivity are primarily localized to the synovium, leading to pain and articular damage, but are also associated with a broader series of comorbidities [27]. Currently, an advanced understanding of the pathologic mechanisms underlying autoreactive CD4+ T cells, B cells, macrophages, inflammatory cytokines, chemokines, and autoantibodies that cause RA has been achieved [28]. The differentiation of follicular dendritic cells is regulated by specific molecules that influence fibroid or lymphoid synovitis, which are related to prognosis in RA

[29]. Significant recent progress in understanding RA pathogenesis has led to improved treatment and quality of life [30].

Genetic Triggers of rheumatoid arthritis

Numerous studies have highlighted significant genetic involvement in RA pathogenesis, with main genetic risk factors including human leukocyte antigen (HLA) genes and non-HLA variants, which interact in complex ways with immune dysregulation, antigen presentation, and signaling pathways [31]. Studies have reported considerable genetic variation in the human species, which renders heterogeneous associations with disease activity and phenotype in RA [32]. The etiology of RA is complex, involving genetic factors such as HLA-DR4, HLA-DR1, HLA-DRB1, and PTPN22, which increase disease risk [33]. The main genetic indicators for RA susceptibility are HLA-DRB1 and PTPN22, and smoking greatly increases the risk in those who are genetically susceptible to the condition [34]. Other genes that were identified to have a causal relationship with RA include AP4B1, GGA2, KEAP1, PTPN22, REG4, and TRAV38-2DV8 [35]. These findings provided novel therapeutic targets for the treatment of RA. More than 100 genetic loci have been identified in RA patients, including those genes involved in various mechanisms, such as loss of self-tolerance, autoimmune antibody production (HLA-DRB1, HLA-DPB1), inflammatory signaling and bone destruction (PTPN22, CCR6), complications (HLA-DQB1, IRF5), and differential drug responses (HLA-E, NKG2D) [36]. These enhanced our understanding of RA pathogenesis and provided insight into the possibility of individualized diagnosis and treatment of the ailment. RA is triggered by a genetic predisposition and environmental factors, and the disease case accumulates within families, thus revealing the impact of candidate gene missense variants on the disease course and elucidating the molecular pathogenesis of RA [37]. It is possible to enhance RA medications and provide tailored care to each individual [38]. More than 100 non-HLA loci have been identified as associated with various immunological processes in the development of RA [39]. From the foregoing, it is clear that research into the genes, pathways, and pathogenic immune cell subsets in RA has advanced our understanding of the mechanisms underlying pathogenesis [40].

Environmental Triggers of rheumatoid arthritis

Several factors, such as cigarette smoking, airborne pollutants (silica, solvents, asbestos, and metals), alcohol consumption, ultraviolet light, microbial exposure, occupational exposures, obesity, chronic stress, and inadequate vitamin D intake, are recognized risk factors for rheumatic diseases, including RA [41,42,43]. Natural environmental factors, such as average temperature at birth, birthplace latitude, and sunshine rate, also showed a nonlinear relationship with the risk of RA [44]. In an earlier study, environmental factors like climate change, pollution, and disease-causing microbes, and poor lifestyle choices such as smoking and poor nutrition were reported to result in chronic diseases like RA [18].

Autoantibody Production in rheumatoid arthritis

The risk of developing RA is increased by the presence of autoantibodies in healthy individuals; however, the rate of progression to RA within these populations is highly variable [45]. The innate immune system and the more recently evolved adaptive immune system prevent the development of autoantibodies and enable tolerance by preventing self-antigens from mounting an immune response while non-self-antigens mount an appropriate response [46]. An autoantibody family studied extensively for both its diagnostic potential and the biological/immunological pathways underlying its induction is the Anti-Citrullinated Protein Antibody (ACPA) response in RA [47]. In a study, 51 IgM and 25 IgG autoantibodies, Anti-vitronectin (VN), anti-glutathione S-transferase P1 (GSTP1), and anti-calmodulin, which included anti-complement 1 protein, anti-high-mobility group box 2 (HMGB2), anti-histone 4, anti-nucleosome, anti-fibrinogen, anti-profilin 1, anti-collagen V, anti-KU (P70/P80), anti-La/SSB, and anti-fibrinogen IV were identified in the synovial fluid of patients with RA [48]. Autoantibodies are a hallmark of RA, with rheumatoid factor (RF) and antibodies against citrullinated proteins (ACPA) among the most recognized [49,50]. The production of autoantibodies has been linked to severe symptoms, such as joint injury and increased mortality, because autoantibodies against citrullinated peptides (ACPAs) can form immune complexes with citrulline-containing antigens, which subsequently bind to rheumatoid factors (RF), thereby activating the complement system [22].

Signaling Pathways pathogenesis in rheumatoid arthritis

Main signaling pathways related to RA include: The Janus-activated Kinase (JAK), Signal Transduction and Activator of Transcription (STAT), Notch, Mitogen-Activated Protein Kinase (MAPK), Wingless/Integrated (Wnt), phosphatidylinositol 3 kinase (PI3K), and spleen tyrosine kinase (SYK) signaling pathways [22,51,52]. Related signaling pathways are often the potential targets for drug discovery. The JAK-STAT signaling pathway is one of the most crucial pathways in cytokine signaling [51]. This pathway is involved in many pathological conditions and appears to be important in abnormal hyperplasia of RA FLS, synovial inflammation, and bone destruction [52]. The MAPK signaling pathway regulates various cellular activities, including gene expression, metabolism, migration, survival, cell cycle progression, apoptosis, and differentiation, all of which play major roles in the pathogenesis of RA [53]. The PI3K-AKT pathway is an intracellular signaling pathway that regulates proliferation, metabolism, angiogenesis, and cell survival in response to extracellular signals; it involves the genes PI3K and Protein Kinase B (PKB) [54]. SYK is a central molecule in β-cell receptor signaling; in RA patients, the level of phosphorylated SYK in peripheral blood β cells is elevated, and patients are often positive for autoantibodies against citrullinated peptides [55]. The Wnt signaling pathway normally functions in multiple physiological and pathological processes, and the Wnt/β-catenin signaling pathway is activated and participates in a variety of pathological processes, including maintenance, differentiation, proliferation, and self-renewal in RA [56]. Notch signaling expression and activation stimulate synoviocytes, macrophages, and fibroblast-like synoviocytes to secrete pro-inflammatory cytokines that exacerbate RA, and Notch signaling may represent a new therapeutic target of RA [57]. Transcription factors such as NF-κB, Nrf2, HIF, and AP-1 are involved in the pathogenesis of RA [58]. The expression of NF-κβ in the synovium of RA patients was significantly increased, and activated NF-κβ induces the generation of numerous pro-inflammatory cytokines, notably interleukins (IL-1β, IL-6) and tumor necrosis factor-α (TNF-α), thus accelerating the development of RA [59].

Cytokine network involvement in rheumatoid arthritis

The cytokines tumor necrosis factor (TNF)-α and interleukin IL-6 play central role to the pathogenesis of RA, but recent research has revealed that other cytokines such as IL-7, IL-17, IL-21, IL-23, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1β, IL-18, IL-33, and IL-2 are also implicated through triggering synovial cell proliferation and causing damage to both cartilage and bone [60]. In the preclinical phase, cytokines notably IL-12, IL-6, IL-21, and TGF-β, promote Tfh and Tph cell differentiation, helping autoreactive β cells to produce Anti-Citrullinated Protein Antibodies (ACPA); whereas during the clinical phase, TNF-α, IL-6, and IL-1β drive synovitis by activating macrophages and fibroblast-like synoviocytes, and also promote RANKL (Receptor Activator of Nuclear factor κβ Ligand) expression and osteoclast differentiation [61,62,63]. Depression is usually a consequence of systemic inflammation, especially when the cytokine network is dysregulated. IL-17 promotes the progression of RA to osteoporosis [64]. RA-associated cytokines such as IL-10, IFNα/β, and TNF modulated immune checkpoint receptor (IR) expression, while IL-6, IL-10, IL-12, IFNs, and TNF increased expression of TIM-3, PD-1, LAG-3, and CD28 in response to RA synovial fluid, suggesting a role for these cytokines in the regulation of disease pathology [65]. From studies to date, it is clear that cytokines and cytokine receptors are important drug targets for the treatment of RA [66].

Synovial Hyperplasia and Pannus Formation in rheumatoid arthritis

In RA, chronic inflammation, immune dysregulation, genetic factors, and angiogenesis lead to synovial hyperplasia, which is the main cause of bone damage because it involves the abnormal proliferation of the synovial membrane, leading to inflammatory joints and significantly contributing to joint damage and dysfunction [67,68]. Abnormal synovial hyperplasia and cartilage destruction in a joint cavity were identified to be among the factors responsible for the pain and disability in RA [69]. One of the effects of RA is the appearance of pannus, which is an aggressive structure in the inflamed rheumatoid joint that invades the cartilage and bone, thus causing irreversible joint damage [70,71]. Proliferation of synovial tissue, pannus formation, and irreversible damage to joint cartilage and bone cause progressive joint destruction and deformities, contributing to a substantial portion of the global disability burden [72].

Bone Erosion in rheumatoid arthritis

Computed tomography (CT) imaging characteristics of bone erosion in RA patients were closely associated with the expression of rG4s-regulated RA-related inflammation-related Differentially Expressed Genes (irDEGs) [73]. In RA patients with disease activity managed with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate (MTX), predictors of new bone erosion included seropositivity, elevated inflammatory markers (CRP, ESR), and baseline ESR ≥ 3 [74]. Core metabolites implicated in bone erosion included mangiferic acid, O-Acetyl-L-carnitine, 5,8,11-eicosatrienoic acid, and 16-methylheptadecanoic acid, which were used to develop a standardized bone erosion risk score (BERS) to assess radiographic progression [75]. Bone erosion of periarticular cortical bone in patients with RA results from excessive local bone resorption and inadequate bone formation, which are triggered by synovitis [76]. In RA, bone tissue is characterized by uncoupling of bone formation and resorption, leading to a significant increase in osteoclastic activity and an erosive bone phenotype that clinically manifests as skeletal erosions [77]. Erosion-free patients had a less severe disease course, as reflected in disease activity, and were more often seronegative than those with erosive disease [78].

Hypoxia in rheumatoid arthritis

The oxygen level in the joint cavity of a RA patient is significantly reduced, and the hypoxic microenvironment has become a key factor in the pathogenesis and progression of RA, as hypoxia affects signaling pathways and cell function, thereby aggravating the onset and progression of RA [79]. Hypoxia, which can result from high-altitude surroundings and intestine, is a distinct state in the synovium of RA, and it can aggravate arthritis [80]. RA synovial inflammation, pannus formation, cartilage destruction, and bone erosion were linked to increased oxygen consumption, resulting in hypoxia within the inflammatory area, and the hypoxia-inducible factor (HIF) was reported to be associated with adaptation to the hypoxic microenvironment in the RA synovium [81]. Although new blood vessels deliver oxygen to the augmented inflammatory cell mass, the neovascular network is dysfunctional and fails to restore tissue oxygen homeostasis, leaving the rheumatoid joint as a markedly hypoxic environment [82,83]. During the development of RA, a hypoxic and inflammatory situation in the synovium maintains reactive oxygen species generation, which has been shown to be associated with synovitis in RA [84]. Hypoxia-inducible factor-1α (HIF-1α) functions as a master epigenetic regulator of synovial angiogenesis, metabolic reprogramming, cytokine production, citrullination, migratory and invasive capacity in fibroblast-like synoviocytes (FLS), and regulation of intestinal barrier integrity [85]. Consequently, current RA treatments target HIF-1α.

Angiogenesis in rheumatoid arthritis

Angiogenesis, the formation of new blood vessels, is important for leukocyte extravasation and thus the pathogenesis of RA, as the new blood vessels formed maintain a chronic inflammatory state by transporting inflammatory cells to the site of inflammation [86]. In RA, experimental and translational studies suggest that enhanced activity of the renin-angiotensin system within synovial tissue is associated with angiogenesis, synovial inflammation, fibroblast-like synoviocyte survival, and bone erosion through pathways involving nuclear factor kappa β (NF-kβ), mitogen-activated protein kinase (MAPK), and receptor activator of nuclear factor kβ ligand (RANKL)/Wingless-related integration site (Wnt) signaling pathways [87]. Compounds such as NF-κβ-inducing kinase inhibitor (NIKi), tofacitinib, and fluciclatide were used for safe diagnostic targeting of microdose in RA [88]. Natural medicines have a long history of treating RA, and numerous reports have suggested that they exhibit strong inhibitory activity against synovial angiogenesis, thereby slowing the progression of RA [89]. The pathogenesis of RA involves both innate and adaptive immunity, as well as angiogenesis, resulting in a complex network of inflammatory cytokines that contribute to synovial cell proliferation, cartilage, and bone damage [90]. Angiogenesis is a fundamental process in both physiological processes, such as tissue repair and regeneration, growth, and embryogenesis, and in pathological conditions, allowing tumor development and the progression of inflammatory arthritis [91]. Numerous angiogenic mediators, including growth factors, cytokines, chemokines, proteases, extracellular matrix macromolecules, cell adhesion molecules, and basic fibroblast (bFGF), epidermal (EGF), and placental (PlGF) growth factors, promote synovial angiogenesis in RA [92,93].

Pathological Significance and Clinical Consequences of Rheumatoid Arthritis

Bone destruction: Synovial **Cluster of Differentiation 68** (CD68)- positive cells and synovial macrophages were independent risk factors for progressive bone erosion in RA [94]. Synovitis and pannus lead to the accumulation of inflammatory cytokines, which erode bone tissue, resulting in joint dislocation, deformity, and disability [94].

Systemic manifestations: RA is a systemic autoimmune disease predominantly involving small joints and causing joint deformity and functional loss with systemic manifestations, such as pulmonary, cardiovascular, and neurologic involvement [95]. There was evidence of systemic inflammation and signatures of activation in naïve T and β cells of at-risk individuals during progression to clinical RA [96]. Symmetric inflammatory polyarthritis is the most prominent manifestation of RA, although the disease can affect any organ system, including hematologic, neurological, cardiac, pulmonary, skin, ocular, and renal systems [97]. RA was also noted in another study to be marked by inflammation and hyperplasia of the synovial membrane, the production of autoantibodies (such as rheumatoid factor and anti–citrullinated protein antibody [ACPA]), destruction of cartilage and bone leading to deformity, and various systemic manifestations, which encompass cardiovascular, pulmonary, psychological, and skeletal issues [68].

Increased Mortality: In a study done in Australia, a total of 1895 RA patients were included; 74% were female, with a baseline median age of 50 years, and 204 deaths as a result of respiratory conditions, which were primarily attributable to pneumonia and interstitial lung disease [98]. The number of deaths was doubled by the presence of RA in patients with bronchiectasis [100, 99]. The long-term prognosis of RA has improved in recent years due to early diagnosis and effective pharmacological treatment, resulting in most RA patients achieving stable clinical remission or experiencing lower disease activity [101]. Over the past 32 years, the global number of RA-associated deaths among individuals aged 20 to

54 years increased by 2.97%, as against the RA-associated death rate which decreased from 0.09 per 100,000 in 1990 to 0.06 per 100,000 in 2021 and the death was higher among females than that among males, with 1542 deaths (females) compared to 766 deaths (males) [13].

Functional Disability: A significant positive correlation was found between the Modified Health Assessment Questionnaire (MHAQ) and various markers of activity, with age, depression, illiteracy, ischemic heart disease, erosions, and subluxations associated with higher MHAQ scores and greater disability [102]. In a study done in Indian rheumatic patients, the mean HAQ-DI score was 0.70 ± 0.83, and functional disabilities, most prevalently eating and personal hygiene, were found to be significantly associated with high rheumatic disease activity [103]. In another study, the participants (90% women, age 58.8 ± 12.8 years) had a mean HAQ-DI score of 1.7 ± 0.5, and majority of them (56%) showed a moderate-to-severe disability, which was associated with advanced age, longer disease duration, unemployment, joint replacements, and outcomes for daily functioning and physical quality of life [104]. Among 204 patients tested with DMARD therapy in a study, clinical remission, structural remissions defined as an increase in modified total Sharp score (mTSS) ≤ 5 per 10 years, and functional remission, defined as health assessment questionnaire-disability index (HAQ-DI) ≤ 0.5, were achieved by 68.1%, 73.0%, and 81.4% of patients, respectively [105]. Among 314 patients with RA who participated in a study, the mean score of HAQ-DI was 0.87 (SD: 0.91); patients in the moderate and high disease activity groups showed significantly reduced health state utility values and HRQoL scores (all $p<0.05$), while there was an increase in HAQ-DI scores, indicating more impairment ($p<0.05$) [106]. In rheumatoid arthritis patients, the five most frequent limited activities in the ICF chapter "Mobility" included "Walking", "Changing basic body position", "Stair climbing", "Grasping", and "Lifting" (axSpA), and "Maintaining a standing position" [107,108]. Patients younger than 65 with RA and new-onset work disability are much more likely to develop functional disability compared to patients without RA, for whom biological age is the major driver of disability [109]. Occupational, personal, medical, and societal factors are the main predictive categories of work disability for people with RA [110].

Epigenetic Regulation: In RA, epigenetic mechanisms, including DNA methylation, histone modifications, RNA editing, and non-coding RNAs, critically shape immune cell activation, differentiation, and effector functions, perpetuating autoimmunity and chronic inflammation [111]. Epigenetic dysregulation stands at the forefront of pathogenic mechanisms underlying widespread autoimmune diseases, including RA at multiple stages, encompassing disease etiology, pathogenic mechanisms during disease development, and disease activity and progression as biomarkers [112]. Epigenetic alterations, including dysregulated microRNA (miRs) expression, DNA methylation, and histone acetylation, also play important roles in RA onset and pathogenesis by modulating the post-translational expression of key genes involved in synovial inflammation and joint destruction [113,114]. Through epigenetic remodeling, environmental, metabolic, and inflammatory inputs are transduced into changes in gene expression. The epigenome functions simultaneously as a sensor and effector of immune state, converting fluctuations in cytokine exposure, oxidative stress, and metabolite availability into heritable transcriptional programs that stabilize effector differentiation and, at the same time, erode tolerance [115]. Integrative multi-omic studies now position epigenetic drift as a defining hallmark of rheumatic autoimmunity. Epigenetics is the alteration in gene expression and function without changes in DNA sequences, leading to heritable phenotypes, DNA methylation, post-translational protein modifications, and post-transcriptional gene regulation [116]. Epigenetics plays a key role in autoimmune diseases, including RA. Epigenetic alterations have been proposed as diagnostic and therapeutic biomarkers, while epigenetic mechanisms are thought to contribute to the pathogenesis of RA. Epigenetic regulators coordinate gene expression and, in the case of inflammatory diseases, regulate the expression of a broad range of inflammatory molecules [117].

Therapeutic Targets

With the sustained development of disease-modifying antirheumatic drugs (DMARDs), significant progress has been made in preventing and reducing disease activity in RA patients. Unfortunately, some patients still show limited response to DMARDs, necessitating the identification of new targets and novel therapies [118]. A large number of clinical trials have been conducted by scientists and clinicians to test various agents for the treatment of RA. Some of these agents, approved for clinical use, include nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylate, naproxen, ibuprofen, and etodolac, which are used to alleviate pain, reduce swelling, and decrease inflammation. NSAIDs exert their effects by inhibiting the enzymatic activity of cyclooxygenase (COX), which is involved in prostaglandin (PG) synthesis [119]. Inhibition of COX-2 by NSAIDs blocks PG production at sites of inflammation. In addition, corticosteroids, such as glucocorticoids, are potent anti-inflammatory drugs that modulate gene expression by binding to glucocorticoid receptors and exerting anti-inflammatory and immunosuppressive effects. Owing to the adverse effects of NSAIDs and corticosteroids, disease-modifying antirheumatic drugs (DMARDs), a class of immunosuppressive and immunomodulatory agents, like methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, chloroquine, and gold salts, were developed to prevent and relieve RA aggression. If a patient shows nonresponse to csDMARDs, biological DMARDs, or targeted synthetic DMARDs, these agents should be added. bDMARDs such as adalimumab, infliximab, certolizumab, canakinumab, tocilizumab, sarilumab, and secukinumab are monoclonal antibodies and have target tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, and IL-17 [120]. tsDMARDs also have specific targets, such as janus kinases (JAK), which are targets of tofacitinib, baricitinib, filgotinib, upadacitinib, and decernotinib [121]. Other targets which were also identified include protein targets like IL-4, IL-10, IL-15, IL-17, IL-18, IL-23, interleukin-1 receptor-associated kinase (IRAK)-4, lipoxins (LXs), platelet-activating factor (PAF), and leukotrienes (LTs), nitric oxide (NO), and reactive oxygen species (ROS) [122]. Besides, an increasing number of studies show that epigenetic regulators play important roles in RA, like non-coding RNAs, DNA methylation, RNA methylation, and histone modifications [123]. These targets have been explored by researchers to develop some new agents for RA. A study by Anandan and Narayanan [124] identified pathways that have been successfully targeted for therapy, including cytokines, tumor necrosis factor (TNF-α), and interleukin 1 (IL-1), β cells, osteoclasts, and costimulatory molecules. Consequently, the biologic agents, such as anti-TNF agents, IL-1 inhibitors, β-cell-depleting antibodies, and selective costimulation inhibitors, are showing promise in improving outcomes in patients who could not be treated with methotrexate. Novel Molecular Targets have also been identified to enhance RA treatment. These targets include: Bruton's Tyrosine Kinase (BTK) Inhibitors which play a critical role in β cell activation and autoantibody production [125]; Mitochondrial Complex I Inhibitor Leramistat (MBS2320) is an investigational small molecule that targets mitochondrial complex I with preferential activity in osteoclasts, thereby offering a dual mechanism of anti-inflammatory and anti-resorptive action [126]; and NOD-, LRR-, and Pyrin Domain-Containing Protein 3 (NLRP3) Inflammasome Inhibitors. The NLRP3 inflammasome is a key intracellular sensor that contributes to innate immune activation by facilitating the maturation and release of IL-1β, a potent pro-inflammatory cytokine [127]; Regulatory T Cells (Tregs) and Immune Checkpoints Enhancing Treg function are innovative strategies for modulating immune tolerance in autoimmune diseases [128]; Targeted β and T Cell Therapies Telitacicept is a fusion protein that inhibits the TACI (transmembrane activator and CAML interactor) receptor expressed on β cells. This receptor mediates signaling through BAFF and APRIL, promoting β cell maturation and immunoglobulin production—processes often dysregulated in autoimmune diseases such as RA [129]; Spleen Tyrosine Kinase (SyK) Inhibitors SyK is a cytoplasmic non-receptor tyrosine kinase that plays a pivotal role in the intracellular signaling cascades downstream of immune receptors, particularly within β cells, Fc receptors, and integrins. Through these pathways, SyK modulates the activation, proliferation, and cytokine release of multiple immune cell populations. In the setting of RA, aberrant SyK signaling has been linked to the increased production of pro-inflammatory cytokines and matrix metalloproteinases, especially in response to TNF, thereby contributing to joint destruction and disease progression [130]; Anti-Granulocyte–Monocyte Colony-Stimulating Factor (GM-CSF) Antibodies plays a critical role in the differentiation and activation of hematopoietic cells, particularly granulocytes and monocytes, and is implicated in the immune system dysregulation observed in inflammatory and autoimmune diseases. Elevated GM-CSF levels in inflamed tissues contribute to RA pathogenesis. Multiple anti-GM-CSF antibodies have been investigated for RA treatment [131]; Nuclear Factor-Kappa β (NF-κβ) Inhibitor, Iguratimod, is a csDMARD approved in Japan since 2012 for the treatment of RA. It suppresses β cell activity by inhibiting pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, and IL-17, and by downregulating NF-κB signaling, thereby reducing immunoglobulin production. By disrupting NF-κβ-dependent signaling cascades, iguratimod effectively downregulates pro-inflammatory cytokine production and attenuates immune-mediated tissue damage [132].

Pharmacological Treatments of Rheumatoid Arthritis

Due to its complexity, which is based on an incompletely elucidated pathophysiological mechanism, good RA management requires a multidisciplinary approach. The clinical status of RA patients has improved in recent years due to advances in diagnosis and treatment, enabling reduced disease activity and prevention of systemic complications. The most promising results were obtained by developing disease-modifying anti-rheumatic drugs (DMARDs), the class to which conventional synthetic, biologic, and targeted synthetic drugs belong [133]. Pharmacological agents that help maintain joint function can be classified as conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and targeted synthetic DMARDs, which are included in a new class of nonbiologic DMARDs by the American College of Rheumatology (ACR) [12]. DMARDs are pharmacological agents that are used to promote remission by suppressing autoimmune activity and by delaying or preventing joint degeneration. The treatment should be initiated as soon as possible because early implementation leads to better results. This is due to the fact that DMARDs are slow-acting drugs with a delayed onset of between 6 weeks and 6 months. DMARDs have been classified as conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) [134]. csDMARDs are a heterogeneous class of drugs including methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ), and sulfasalazine (SSZ), which are more frequently used than other agents with a lower efficacy and safety profile, such as gold salts, azathioprine, d-penicillamine, cyclosporine, minocycline, and cyclophosphamide. Their mechanisms of action lead to a non-targeted suppression of the overactive immune system [135]. DMARDs can take several weeks or months to demonstrate a clinical effect. DMARDs include methotrexate, sulfasalazine, leflunomide, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, abatacept, rituximab, tocilizumab, anakinra, and antimalarials. Other immunomodulators are occasionally used, including azathioprine and cyclosporine. Because cartilage damage and bony erosions frequently occur within the first two years of disease, rheumatologists now move aggressively to a DMARD agent early in the course of disease, usually as soon as a diagnosis is confirmed. TCM has gradually emerged as a vital source of novel therapeutic agents for RA, attributed to its multifunctional bioactivities and ability to target multiple pathways. In addition, modern approaches such as vaccines, nanodrug delivery systems, gene therapy, and cell therapy have been developed for RA treatment [21]. Five JAK inhibitors show comparable efficacy to bDMARDs, and the latest ones are effective for overcoming difficult-to-treat RA regardless of prior medications. Advances in therapeutic strategies, including differential drug use and de-escalation of treatment after remission induction, are prioritized [136]. Smart hydrogels have emerged as a promising platform for RA treatment due to their unique three-dimensional hydrophilic networks, excellent biocompatibility, and tunable physicochemical properties [137]. There have been recent findings on the different classes of RA therapies, including conventional and modern drug therapies, as well as emerging options such as phyto-cannabinoid and cell- and RNA-based therapies [138].

Non-pharmacological Management of rheumatoid arthritis

With knowledge of RA risk factors, researchers can offer solutions to prevent RA, which may be an important aspect of the general management of RA. Four levels of prevention have been shown, including primary, secondary, tertiary, and clinical. Primary prevention focuses on preventing pathological processes from beginning; secondary prevention manages risk factors to detect and reduce them; tertiary prevention focuses on damage-limiting mechanisms; and clinical prevention aims to reduce complications and prevent relapses [12]. Screening strategies of people at risk of developing RA may result in lower incidence and prevalence rates. Blood relatives, twins of RA patients, and seropositive individuals should be closely monitored because they are at risk [139]. The goals of nonpharmacological approaches are to decrease anxiety and depression, to reduce pain, and to increase mobility. Polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have attracted greater attention due to their links to a range of brain disorders, including anxiety and depression [140]. Rest, occupational therapy, physical exercise, and surgery can also be useful. Most studies evaluating the role of physical activity and psychological interventions in RA-related fatigued patients have demonstrated their effectiveness in relieving stress on inflamed tissues and slowing the progression of the disease, with a consequent increase in joint function [141]. Joint surgery is used only in severe stages of RA to provide pain relief and restore the function of joints. Due to recent advances in surgery, numerous procedures are available, including tenosynovectomy, radio synovectomy, arthroscopy, osteotomy, joint fusion, metatarsal head excision, arthroplasties, and total joint replacement [12]. Scientific evidence suggests that massage, positioning, hot and cold therapy, acupuncture, transcutaneous electrical nerve stimulation, and progressive muscle relaxation are complementary therapies that might be useful in nonpharmacological pain management [142]. Nonpharmacological approaches should be used alongside pharmacological treatments to maximize therapeutic success. Some non-pharmaceutical interventions in RA, such as complementing with various dietary, fatty acid, or vitamin supplements, may further reduce the disease burden [143]. As pharmacological treatment options are often limited in D2TRA, the need for non-pharmacological treatments (NPT) is even more pronounced. The mechanisms of action of non-pharmacological treatments are not well investigated, as they appear to have complex, holistic effects on the immune, neural, and endocrine systems, which can provide significant additive benefit when combined with targeted pharmacotherapies in the treatment of D2TRA [144].

Surgical Interventions in rheumatoid arthritis

Despite advancements in treatments like disease-modifying antirheumatic drugs that delay disease progression, surgical interventions are often necessary to improve the quality of life in RA patients. A comprehensive evaluation of RA elbow considered various surgical options tailored to specific symptoms, including synovectomy for persistent pain due to synovitis, capsulotomy and osteophytectomy for limited range of motion, cubital tunnel release for ulnar neuropathy, and joint replacement or interposition arthroplasty for advanced joint destruction highlighted the necessity of a multidisciplinary approach, integrating surgical and medical strategies to manage RA elbow effectively [145]. The management of RA is best achieved in a multidisciplinary, integrated manner that encompasses medical optimization, surgical intervention, and advanced rehabilitation strategies [146]. This kind of approach has the highest potential to minimize long-term disability, functional recovery, quality of life, and deal with the difficult and long-lasting burden of RA.

Prognosis and Rheumatoid Arthritis Patient Outcomes

The long-term survival of patients with RA receiving biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in a real-world setting, and the prognostic factors influencing mortality within this cohort were evaluated by collecting patients' data, including demographics, disease duration, prior therapeutic regimens, and global functional status in a seven-year follow-up period, extending from June 2017 to December 2024 [147]. Findings show that the overall survival rate of RA patients was 87.3%, and advanced functional disability and prolonged corticosteroid use were independently associated with higher mortality risk [148]. The evaluation of clinical outcomes in RA patients, including the patient's perspective, can be incorporated into clinical decision-making through instruments that assess disease activity, functionality, disease impact, adherence to treatment, and quality of life [148]. To compare clinical and patient-reported outcomes (PROs) over 5 years between patients with RA in sustained remission (sREM), sustained low disease activity (sLDA) or active disease (AD) in the first year after diagnosis, all patients with RA from the treatment in the Rotterdam Early Arthritis CoHort trial, were studied and patients in sLDA in the first year had worse PROs during follow-up, compared with patients in sREM that have better HRQOL and function, and less pain, fatigue and productivity loss in the years thereafter [149]. In other to characterize patients with RA by number of poor prognostic factors (PPF: functional limitation, extraarticular disease, seropositivity, erosions) and evaluate treatment acceleration, clinical outcomes, and work status over 12 months by number of PPF, biologic-naive patients with diagnosed RA, having 12-month follow up were identified and categorized by PPF (0–1, 2, ≥ 3) [150]. Despite high disease activity and worse clinical outcomes, the number of PPF did not significantly predict biologic/tsDMARD use [150]. Iraqi patients with RA who received earlier treatment with etanercept had superior outcomes compared with those who received later treatment [151]. Another study assessed real-world clinical outcomes and patient-reported outcomes (PROs) in adult patients with moderate-to-severe rheumatoid arthritis who received upadacitinib for 6 months in the UK and noted that ePROs demonstrated a rapid onset of action and meaningful improvements in QOL [152]. Another study done in the UK described the characteristics, treatment patterns, and clinical outcomes of patients who received abatacept in clinical practice and reported that RA patients who received bDMARDs, including abatacept, experienced reduced disease activity [153]. In a retrospective cohort analysis of 184 patients with a new diagnosis of RA, long-term analysis reveals that mortality in RA remains significantly elevated compared with the general population [154]. Patient-Reported Outcome Measures (PROMs) could be an efficient and informative way to assess RA, but due to the remoteness of the consultations, there was insufficient evidence of content validity, which limited the selection of suitable PROMs; therefore, none can be recommended for use [155].

Future Perspectives on Rheumatoid Arthritis

Despite all the improvements in the treatment of RA, we are still not able to prevent or cure the disease. Diagnostic delays and expensive therapies are still a major hindrance for many patients. Even in first-world countries, the treat-to-target principle and the goal of disease remission are often missed [156]. Due to the high complexity of the interplay between genetics and epigenetics, a genuinely individualized therapy for RA is currently not possible; instead, standard therapeutic algorithms are used, but they are not tailored to the individual characteristics of the patient [157,156]. The development of new tools, including the Disease Activity Score derivative for 28 joints (DAS28), the Simplified Disease Activity Index, and the Clinical Disease Activity Index, that can adequately monitor disease activity has facilitated new treatment strategies to arrest RA before irreversible joint damage occurs [158]. Long-term use of such types of pharmacological drugs is associated with serious side effects. As a result, herbal remedies, lifestyle, nutritional, probiotic, dietary, and psychological interventions provide a rich source of anti-arthritic agents for RA management [159]. Novel cell-based therapies, such as chimeric antigen receptor T cells and T cell engagers, have the potential to enable durable, drug-free remission, thereby further optimizing RA management and improving patient outcomes [24]. Nanotechnology offers an opportunity to overcome the limitations of combination drugs by improving the solubility and bioavailability of combination drug formulations and enhancing joint selectivity for inflamed joints, as seen in nanoformulations of prednisolone and methotrexate [160]. Research into the molecular mechanisms of immunological diseases and the development of more specific therapies are advancing rapidly, and this may provide a better paradigm for understanding the pathogenesis and the prospects for interventional immunotherapy of RA [161]. Due to their adjustable surface properties and similar size, custom-designed nanoparticles can now interact with cellular targets and diverse diseases more effectively, ensuring that pharmaceuticals are delivered only to the intended areas, minimizing side effects and unintended consequences [162]. Emerging therapies, including small-molecule inhibitors, targeted biologics, cell-based therapies, and gene-editing technologies, have shown promise in preclinical and early clinical trials and are expected to improve outcomes for patients with RA [163]. Digital health records and advanced diagnostic testing offer significant potential to improve patient outcomes and decision-making by using AI tools such as machine learning (ML) and deep learning to predict outcomes and inform decisions [164]. While not proven in controlled clinical trials, observational studies suggest exercise, weight loss, and smoking cessation may reduce progression to clinical RA [165]. Evidence-based rehabilitation could play a critical role in improving the quality of life for people with RA diseases and promoting their healthy aging [166]. In the initial phase, management of RA depends primarily on pharmacological therapy, but as the disease progresses, surgical correction of deformity, occupational therapy, and physiotherapy come to play an increasingly important role [167]. Current therapeutic developments include the development of additional biologics with various specific targets, the development of small-molecule compounds with similar efficacies, and entirely new approaches to treat autoimmune inflammatory diseases such as RA [168]. Artificial intelligence is an appropriate solution to further improve radiographic scoring, and by fully leveraging its power, faster, more sensitive scoring could enable the ongoing development of effective treatments for patients with RA [169].

CONCLUSION

Researches have been able to elucidate the etiology of RA, and many treatment intervantions have been proffered, including Pharmaceutical and non-Pharmaceutical approaches. Yet, a definitive cure of the ailment has not been achieved. A lot of studies are still ongoing with the intention of discovering a lasting solution to this autoimmune problem –rheumatoid arthritis.

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