Int J Biol Med Res. 2024; 15(2): 7802-7806

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Review article

Immunotherapy of Rheumatoid Arthritis: A Review

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ARTICLEINFO

Keywords:
Rheumatoid arthritis
chronic inflammation
Immunotherapy

ABSTRACT

Background and Aims-Immunotherapy is a revolutionary treatment approach for rheumatoid arthritis. However, based on our knowledge, the disease is not well studied. Understanding the pathophysiology, possible diagnosis, and management interventions for rheumatoid arthritis is crucial for improving the quality of life for individuals with the disease. This study was conducted based on the PRISMA guidelines for review. Our data showed that immunotherapy has demonstrated significant potential in the management of rheumatoid arthritis by specifically targeting dysregulated immune responses implicated in the disease pathogenesis. TNF-α inhibitors, IL-6 receptor antagonists, B-cell depletion therapy, and JAK inhibitors have all shown efficacy in reducing inflammation and improving clinical outcomes in rheumatoid -arthritis patients. In addition, by targeting the key immune pathways, immunotherapy demonstrated a substantial impact in reducing the disease activity and slowing the progression of joint damage. Consequently, immunotherapy is a valuable therapeutic option for rheumatoid arthritis patients who do not respond adequately to the traditional treatment modalities. As our understanding of the immunological processes in rheumatoid arthritis deepens, further advances in immunotherapy are expected, providing hope for more personalized and effective approaches to managing the chronic autoimmune disease.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects the joints region of the body. In year 2019, according to the World Health Organization (WHO), about 18 million people in the world particularly women older than 55 years were living with rheumatoid arthritis. The body's immune system attacks joint tissues that causes chronic pain and inflammation. The disease could parts of the body, including the skin, eyes, lungs, heart, nerves, and blood which may cause the red blood cell count to be low with inflammations around the lungs and heart, often the symptoms seed gradually over weeks to months [2].

Immunotherapy such as biologic DMARDs are proven to be effective in the management of RA [3, 4]. It is a biological therapy for the treatment of disease by activating and suppressing the immune system of the body. Smolen et al. [5] reported that biologic DMARDs targeting TNF-alpha, interleukin-6, and B-cells have demonstrated significant clinical benefits in reducing RA severity. Immunotherapy is used for allergies, and autoimmune disorders such as Crohn's disease, Hashimoto's thyroiditis and rheumatoid arthritis, and certain cancers [6]. In addition, another study by Fleischmann et al. [7] evaluated the use of JAK inhibitors, a form of immunotherapy in the treatment of RA.

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To stop the autoimmune attacks, immunotherapy protects the body from its attacks by interrupting the autoimmune responses [8]. However, after many years of asymptomatic autoimmunity and progressive immune system remodeling, tissue tolerance erodes, joint inflammation emerges as tissue-invasive effector T- cells, and the protective joint-resident macrophages fail [9].

Justification of the study

The epidemiology of RA is not well studied, but some reports have been done to estimate its prevalence and impact. According to a systematic review and meta-analysis protocol published in 2020, there is a need to update the existing data on RA which are based on old and limited studies [3, 10]. The authors searched various databases for observational studies addressing RA and hope to provide more consistent and reliable estimates of RA prevalence and burden.

Another article published in 2022 reported that there are rising cases and burden of RA in Nigeria, and called for more awareness and management of the disease condition [11]. The article cited some challenges faced by RA patients in Nigeria, such as lack of access to affordable and effective medications, lack of rheumatologists and specialized care centers, lack of awareness and education among the public and health professionals, and stigma and discrimination. The article also mentioned some initiatives to address these issues, such as Project Afya, a patient assistance program launched by Pfizer to improve access to life-saving medications and RA management.

Furthermore, a review published in 2020, discussed some of the unmet needs in managing RA in sub-Saharan Africa, including Nigeria. We highlighted some of the gaps in the diagnosis, treatment, monitoring, and research of RA in this region. Moreover, we suggested some of the possible solutions, such as improving health infrastructure, train-

ing more rheumatologists and allied health professionals, implementing evidence-based guidelines and protocols, increasing funding and collaboration for research, and engaging patients and stakeholders in advocacy and policy-making [12].

In addition, a news article published in 2022 emphasized the importance of awareness and early diagnosis for reducing the prevalence of RA. The article quoted some experts who explained the symptoms, risk factors, prevention, and treatment of arthritis and also urged the government and relevant agencies to provide more support and resources for arthritis care.

Epidemiology of RA

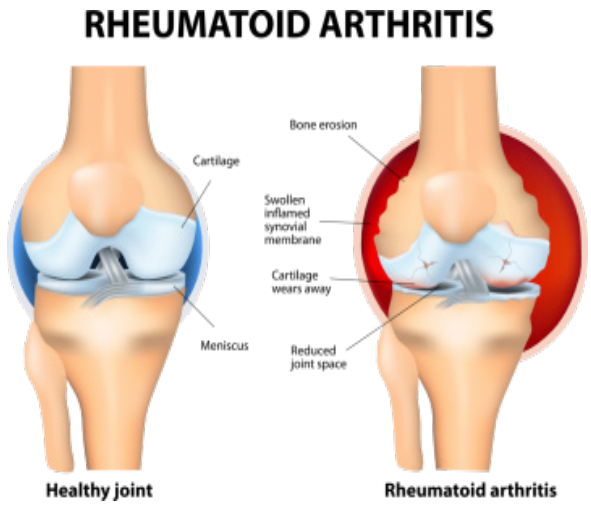
According to the WHO, Rheumatoid arthritis is a chronic inflammatory disease that affects the joints and other body systems. It is one of the most common autoimmune diseases, affecting about 0.46% of the global population. RA is characterized by inflammation and joint damage, making it a significant public health concern. RA is more common in women than in men, with a female-to-male ratio of around 2 to 3:1. The prevalence of RA varies across different regions and populations. It tends to be higher in developed countries compared to developing countries. A systematic review estimated the global prevalence of RA to be approximately 0.24%, with variation among different regions [13].

RA occur at any age, but it usually starts between the ages of 30 and 50 years. The incidence of RA also varies geographically and among different ethnic groups. A study conducted in the United States showed an annual incidence rate of 41 per 100,000 persons, with higher rates among women and older age groups [14].

Risk factors for RA

Genetic elements is a risk in the development of RA. The Human Leukocyte Antigen (HLA) genes, such as HLA-DRB1 is associated with RA. Furthermore, environmental factors, including smoking and exposure to occupational hazards contributes to the developing RA. Besides, hormonal factors, including reproductive history and menopausal status have also showed to be a risk for RA in women [15].

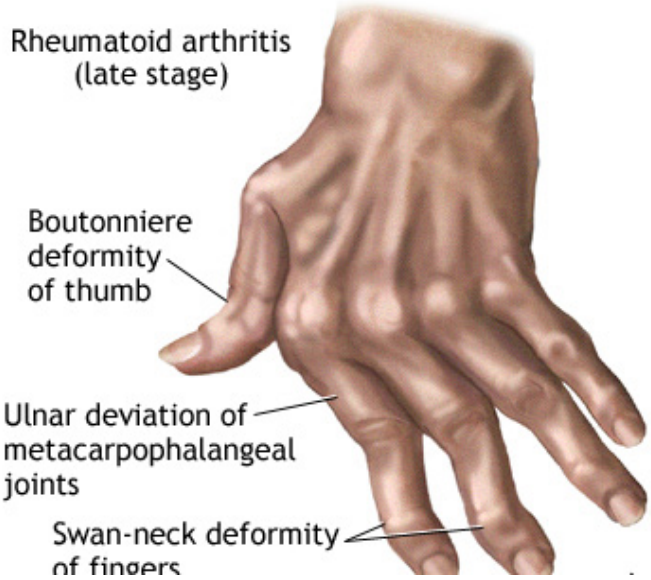
Figure 1: Illustrating rheumatoid arthritis at the joints17



Although additional sex-related factors are likely to be implicated, estrogen on immune function plays a significant role in the RA predominance for the female. Some infectious agents have been proposed as etiologic and contributing agents, including retroviruses, Epstein–Barr virus, bacterial superantigens, and mycoplasma species, as well as organisms such as gut prevotella and oral Porphyromonas gingivalis species.

Cigarette smoking is another most prominent behavioural risk factor for the development of rheumatoid arthritis is. Other factors marginally increase the risk of rheumatoid arthritis, including obesity, low vitamin D levels, and the use of oral contraceptives. In addition, some other factors that decrease the risk of RA include a Mediterranean diet, n–3 fatty acid intake, fish oil supplementation, and alcohol consumption. Although rheumatoid arthritis is pronounced by symmetric arthritis in the small joints of the hands and feet, as the disease progresses any synovial joints can be involved [16].

Figure 2: Illustrating severe rheumatoid arthritis at the fingers 4



RA causes a significant burden of illness for individuals and society. It can lead to pain, disability, reduced quality of life, increased mortality, and high healthcare costs. Early diagnosis and treatment, as well as rehabilitation and assistive products, can help to control the symptoms and prevent the complications of RA.

Etiology of RA

The etiology of RA is complex and possibly involves interactions between multiple genetic and environmental factors. Activation of the immune cells, particularly T cells and B cells, leads to the production of autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs).

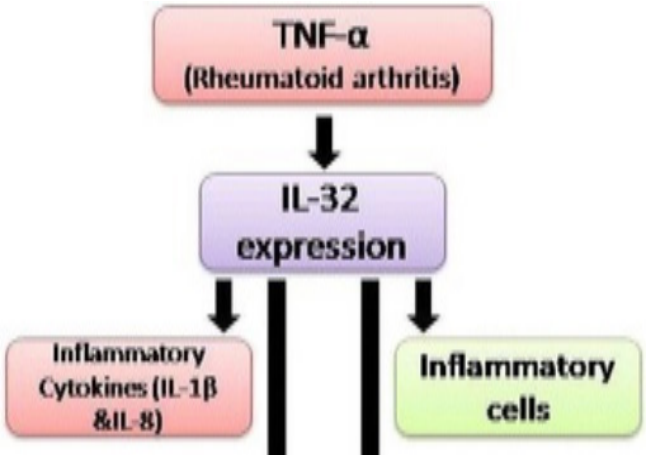
These antibodies contribute to the inflammation and destruction of synovial tissue, causing joint damage and the subsequent clinical manifestations of RA [17]. However, the exact etiology of rheumatoid arthritis is not well understood, it is considered to be a multi-factorial disease that involves both genetic and environmental factors.

Genetic predisposition is crucial in the development of RA. Certain genes, particularly within the major histocompatibility complex (MHC) region are associated with an increased risk of RA. The human leukocyte antigen (HLA) genes, such as HLA-DRB1, have been linked to the development of RA. Genetic variations in other genes involved in immune function and the inflammatory response, such as STAT4 and PTPN22, have also been implicated in RA susceptibility.

Environmental factors triggers RA and the disease progression. Cigarette smoking has been reported to be one of the most proven environmental factor for RA. People who smokes are reliable to developing RA, as well as experiencing more severe disease with poorer treatment outcomes. Periodontal disease, Epstein-Barr virus, and my-

cobacterial infections are known risk factors for RA due to their ability to activate the immune system and inflammatory response. Another risk factor for autoimmune disease is dysregulated immune response, when the immune system attacks its tissues particularly the synovium lining of the joints. In Rheumatoid arthritis, there is an abnormal immune response characterized by the activation of immune cells such as the T cells and B cells which releases inflammatory cytokines and autoantibodies, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies [17].

Figure 3: Illustrating the pathogenicity of RA17



Pathogenicity of RA

The pathogenicity of RA involves multiple mechanisms that contribute to the development and progression of the disease. In RA, there is dysregulation of the immune system, particularly the adaptive immune response. Activated T cells play a central role in the pathogenesis of RA by producing pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) which contribute to chronic inflammation and joint destruction [17]. The B cells are also involved in RA pathogenesis and produce autoantibodies, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, which contribute to tissue damage and inflammation [17].

In synovial Inflammation, the synovium which lines the joints is the primary site of inflammation in RA. Synovial inflammation is driven by the infiltration of immune cells including macrophages, T cells, B cells, and dendritic cells. These cells release pro-inflammatory cytokines and enzymes, such as matrix metalloproteinases (MMPs) that promote the destruction of cartilage and bone [17].In pannus formation, pannus refers to the abnormal proliferation of synovial tissue which invades and damages the surrounding cartilage and bone.

The pannus is formed by activated fibroblast-like synoviocytes (FLS) and inflammatory cells. The pannus releases various inflammatory mediators and proteolytic enzymes leading to the cartilage degradation and erosion of the adjacent bone [18].

In addition, genetic factors contribute to the susceptibility and severity of RA. Specific genetic variations, particularly in certain human leukocyte antigen (HLA) genes such as HLA-DRB1, are associated with an increased risk of developing RA. These genetic factors influence immune dysregulation and the chronic inflammatory response in RA [19].

Clinical presentation of RA

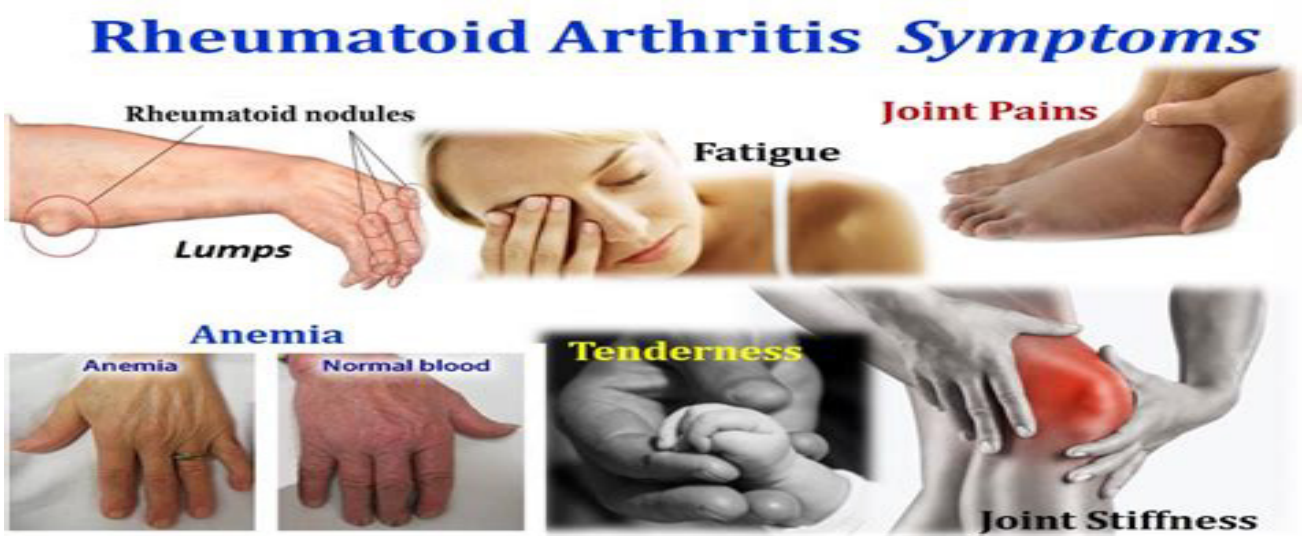
Rheumatoid arthritis is a chronic, systemic, autoimmune, inflammatory disorder of unknown aetiology that primarily involves synovial joints. The arthritis is typically symmetrical and usually leads if uncontrolled to the destruction of the joints due to erosion of cartilage and bone, causing joint deformities. RA most typically presents as polyarticular disease with a gradual onset, but some patients can present with acute onset with intermittent or migratory joint involvement or with mono-articular disease. Systemic symptoms may also be present in RA patients, particularly those with disease onset after age 60 years historically termed "elderly-onset RA" In up to one-third of patients, the acute onset of poly-arthritis is associated with prominent myalgia, fatigue, low-grade fever, weight loss, and depression. Less often, extra-articular manifestations such as nodules or episcleritis may also be present.

Painful joints also make it difficult to exercise, causing weight gain. Overweight RA patients are more likely to develop high cholesterol, diabetes, and heart disease. Chronic inflammation could damage the heart muscle.

Diagnosis of RA

The diagnosis of RA involves a physical examination in alliance with several tests. Some of the criteria for diagnosis include the presence of joint pain, swelling, and morning stiffness for at least six weeks. The detection of Rheumatoid factor (RF) and ACPAs in the blood along with raised levels of the acute phase reactants such as the erythrocyte sedimentation rate and C-reactive protein could support the RA

Figure 5: Illustrating some ways RA affects different parts of the body 19



diagnosis. In addition, imaging modalities such as X-rays, ultrasound, and magnetic resonance imaging (MRI) could aid in evaluating the extent of joint damage [20]. There is no single test that could be used alone for RA diagnosis. Moreover, the early stages of RA are difficult to diagnose since the referred signs are non-specific. Some of the blood tests that could be performed for RA include Erythrocyte Sedimentation Rate (ESR), Rheumatoid factor (RF), C-reactive protein (CRP), Cyclic Citrullinated Peptide (CCP), and Antinuclear Antibody (ANA).

As important in the diagnosis of RA, it is also important to note that none of these tests could conclude that a patient has rheumatoid arthritis. However, the combined results together with other criteria including physical symptoms and genetics to reach a rheumatoid arthritis diagnosis.

Treatments for rheumatoid arthritis

The management of RA is a multifaceted approach that aims to reduce pain, control inflammation, and preserve joint function. Non-pharmacological interventions, including physical therapy, occupational therapy, and patient education, form the foundation of treatment [20]. Pharmacological options include nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and biologic agents, as well as targeted synthetic DMARDs. Newer therapies, such as Janus kinase (JAK) inhibitors, have also demonstrated efficacy in managing RA [21].

Immunotherapy

Immunotherapy is a revolutionary approach to cancer treatment that involves utilizing the body's immune system to recognize and attack cancer cells. Unlike conventional cancer therapies, such as chemotherapy and radiation, immunotherapy aims to stimulate and enhance the natural capacity of the immune system to fight cancer [22]. Immunotherapy works on the principle that the immune system can distinguish between healthy cells and abnormal, cancerous cells. The immune system's capacity to recognize and eliminate cancer cells can be enhanced through various strategies, such as stimulating immune cell activity, improving immune response coordination, or blocking immune checkpoints that inhibit immune cell function. By utilizing these principles, immunotherapy aims to enable the immune system to effectively detect and eliminate cancer cells, potentially providing long-lasting and specific anti-tumour responses [23].

Immunotherapy of RA

Here are some roles immunotherapy plays in Rheumatoid Arthritis;

1. Tumor Necrosis Factor-alpha (TNF-α) Inhibitors:
TNF-α is a key pro-inflammatory cytokine involved in the pathogenesis of RA. TNF-α inhibitors, such as etanercept, infliximab, and adalimumab, are immunotherapeutic agents that block the binding of TNF-α to its receptors. By doing so, TNF-α inhibitors reduce inflammation, alleviate symptoms, and prevent joint damage in patients with RA.

2. Interleukin-6 (IL-6) Receptor Antagonists:
Blockade of IL-6 signalling has emerged as another effective immunotherapeutic strategy in RA. Agents like tocilizumab, sarilumab, and sirukumab disrupt IL-6 signalling pathways, reducing inflammation and ameliorating symptoms in RA patients who do not respond adequately to traditional DMARD therapy.

3. B-Cell Depletion Therapy:
Rituximab, a monoclonal antibody targeting the CD20 antigen expressed on B cells, depletes B cells from the systemic circulation and has shown significant efficacy in RA. This therapy inhibits B-cell activation and limits autoantibody production, thereby suppressing the autoimmune response associated with RA.

4. Janus Kinase (JAK) Inhibitors:
JAK inhibitors, such as tofacitinib and baricitinib, function by inhibiting the intracellular enzymes involved in signalling pathways of several pro-inflammatory cytokines, including IL-6, IL-1, and TNF-α. By downregulating these cytokines, JAK inhibitors modulate the immune response, reduce inflammation, and improve RA-related symptoms.

Conclusion

Rheumatoid arthritis is a chronic inflammatory autoimmune disease affecting the joints. Understanding the pathophysiology, possible diagnosis, and management interventions is crucial for improving the quality of life for individuals. Ongoing research on immunotherapy continues to enhance our knowledge leading to improved treatment strategies aimed at controlling the inflammation.

Acknowledgments

The authors acknowledged the Bingham University for accessing free data services.

Conflict of Interest

Nothing to declare

Funding: None

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