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Rheumatoid Arthritis: Modern Therapeutic Options for Treatment

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Abstract: RA is one of the most prevalent chronic inflammatory diseases that primarily affects the joints and places a heavy burden on both the patient and the community. The treatment is broad, involving several medicines with various dose regimens as well as non-pharmacologic therapies. With the advent of new management guidelines and diagnostic criteria, rheumatoid arthritis treatment options have substantially improved in recent years. However, there are several therapeutic choices available, and new therapeutic approaches are already being developed.

Index Terms **- Rheumatoid Arthritis (RA), Non-pharmacologic therapies, Therapeutic approaches.**

I. INTRODUCTION

Rheumatoid arthritis is one of the most prevalent chronic inflammatory diseases. It primarily affects the joints and places a heavy burden on both the patient and the community. But it can also harm other organs and lead to extra-articular symptoms. Vasculitis, lung involvement, and rheumatic nodules are some of these extra-articular symptoms. With the advent of new management guidelines and diagnostic criteria, rheumatoid arthritis treatment options have substantially improved in recent years. This management revolution has resulted in a dramatic decline in long-term auricular and extra-auricular problems [1] Early identification is considered crucial for the best results, including minimum joint degeneration, DMARD-free remission, radiologic advancement, and cost-effectiveness. Early diagnosis is challenging. It seems, nonetheless, that the patient's and the doctor's delays in prescribing DMARDs are related. Severe diseases can result in extra-articular symptoms as well as other extra-articular symptoms that are not specific [2]. Patients get DMARDs for acute therapy along with or gradually in addition to analgesics like NSAIDs [3]. The study revealed that over the past years, patients with RA had a 1.5-fold higher death risk than the general population. The standardized mortality ratio (SMR) for all-cause mortality, broken down by age, gender, and years, was used to compute the proportion of life-years lost over the research period. The adjustment of all SMR across the period was evaluated using a linear Poisson regressing approach. Then, SMRs for cause-specific mortality were calculated. The population's average age at the outset was 60.4 years old, and a large majority of the patients were female. The estimated SMR for all-cause death over the observation period was 1.54, resulting in a loss of about one life year. The SMR was declining at a 2% annual rate [4]. Rheumatoid arthritis primarily affects women of reproductive age, and as they age, the condition becomes more prevalent. Women are more likely than men to develop the condition. As a result, a significant portion of women who suffer from rheumatoid arthritis conceive, posing a therapeutic challenge for doctors. Rheumatoid arthritis disease activity seems to decrease during pregnancy, then flare up after delivery [5]. Glucocorticoids are utilized to control inflammation as well as immediately reduce pain and swelling. Over the past three decades, there has been a significant advancement in RA treatment methods [6]. Dramatic advances in RA therapy have been made over the past twenty years as a result of the recognition that arthritis is a serious, occasionally fatal condition that necessitates aggressive treatment as well as the development of a sizable number of new therapeutic drugs, both pharmacological and biologic. Although these events occurred simultaneously and were interwoven, they can be partially dissected into discrete parts [7]. A clinical examination is the most common method for identifying rheumatoid arthritis. For the treatment of rheumatoid arthritis, modern therapeutic options are available.

PHARMACOLOGY OF RHEUMATOID ARTHRITIS:

Rheumatoid arthritis (RA) will progress if inflammation is not treated or managed. Rheumatoid arthritis patients who enter remission account for a very tiny percentage of cases. Medications are necessary for the treatment of the symptoms and progression of rheumatoid arthritis. Once a diagnosis has been made, it is recommended to begin therapy. The optimal medical approach to treating rheumatoid arthritis involves taking drugs as well as other therapies. Analgesics, NSAIDs, glucocorticoids, and biologic and non-biologic DMARDs are the five main categories of medicines now in use [8]. Current clinical practice guidelines advise starting biologic medicines if DMARDs are not having the desired effect on the patient. Abatacept is the second most popular first biologic, and it is frequently combined with MTX to treat patients. Tocilizumab appears to be the

most effective biologic as a single medication, according to certain studies. Due to safety concerns, rituximab is rarely utilized as the first biologic therapy, despite the fact that it is still just as effective as anti-TNF. Combinations of these therapies are commonly applied. It is now possible to target particular immune system components that are important for treating RA, such as cytokines, B-cells, chemicals that activate T cells, and antigen presentation cells (APCs) [8].

II. THERAPEUTIC APPROACH IN THE TREATMENT OF RHEUMATOID ARTHRITIS:

3.1. BIOLOGICAL TARGETED THERAPY:

3.1.1. TNF-Inhibitors: In the inflammatory reaction of synovial tissue, TNF and IL1 are the most pro-inflammatory and harmful cytokines. Increased synovial fluid and serum levels are linked to joint deterioration in RA patients, indicating that their activity is dysregulated. TNF inhibition has been discovered to be a rapid and effective strategy to control the symptoms of RA. "Infliximab is a chimeric monoclonal antibody (mAb) that binds to the human IgG1 while also incorporating a mouse TNF antibody's variable region (Fab). It was the 1st anti-TNF drug to be tested for use in the treatment of RA" [9]. According to available data from clinical trials TNF inhibitors safety is as good as that of other anti-rheumatic drugs. Infliximab was the first anti-TNF drug approved for the treatment of RA, and it has undergone the most thorough clinical pharmacological testing. Anti-TNF therapy is one of the most recent breakthroughs in biotechnology, which has cloned cytokines and created inhibitors. It's also one of the outcomes of cytokine research aimed at finding the key, rate-limiting cytokines implicated in disease pathogenesis and potentially useful as therapeutic targets. Clinical trials in related conditions such as Crohn's disease, which have also proven to be incredibly beneficial therapeutically have been inspired by anti-TNF therapy's efficacy in RA [9,10,11,13].

3.1.2. IL-1 Inhibition:
The pro-inflammatory activity of IL-1 can be inhibited as an alternative treatment for RA. 'Anakinra' is a humanized recombinant IL-1 receptor antagonist that suppresses IL-1-mediated signaling by binding to the IL-1 receptor. In clinical trials, 'Anakinra' reduced symptoms and slowed the progression of structural damage in people with moderate to severe RA [9]. 'Anakinra' has a short half-life and needs to be given subcutaneously every day; injection-site pain is a common adverse effect. Despite the fact use as a single monotherapy or in combination with methotrexate, it is rarely used in adult patients with RA because it requires daily injections and has lower response rates than 'TNF-blockers'. In two clinical trials, 'anakinra' was found to be safe and efficient as a monotherapy and in combination with methotrexate for the management of RA. Because of its modest clinical efficacy relative to 'TNF inhibitors' and the need to be injected on a daily basis, Anakinra is only provided to individuals who are intolerant to TNF inhibitors [9,10].

3.1.3. T-Cell Costimulation: As previously stated, T cells triggering the inflammatory cascade in RA. 'Abatacept' is a chimeric human protein that binds to antigen presenting cell and prevents them from engaging with the T-cell receptor [9,12]. It's part of a new family of drugs that prevent 'T-cell activation'. 'Abatacept' is given intravenously once a month a loading regimen of three administrations separated by two weeks. It has been shown in clinicals DMARD to improve the signs and symptoms of RA. The FDA approved this medicine for use in adult patients with RA in 2005, and it was also approved for use in children aged 6 and above in 2008" [9,12]. Abatacept is a single-agent DMARD that can be used alone or in conjunction with other DMARDs. T cell activation is still viewed as a critical event in the beginning and course of RA, despite the fact of the disease. As a result, a variety of 'T cell-targeted' therapeutic options have emerged. Biological therapies that target specific populations of 'activated T cells', as well as pharmacological drugs that 'modify T cells' precisely, are examples of these treatments. T cell-directed biological therapies for RA have been a disappointment due to their lack of efficacy and high toxicity [10,12].

3.1.4. B-Cell–Directed Therapy: Rituximab, a B-cell-targeted therapy, has been studied as a result of a better knowledge of the role of B cells in the inflammatory process of RA" [9]. Depletes peripheral B cells quickly and specifically while causing no harm to plasma cells [9]. Rituximab improved clinical signs and symptoms while also reducing the progression of radiographic disease in multiple clinical trials. Rituximab is administered intravenously as part of a treatment regimen that includes several doses spaced weeks apart. Retreatment is usually given every 6 to 9 months, however it is possible to have longer or shorter periods between courses. Infusion-related symptoms, such as rigors, fever, pruritus, chills, and urticarial rash, with or without accompanying hypotension, were the most commonly reported adverse events in clinical studies. The FDA has approved this medication in combination with methotrexate for adult patients who have had a poor response to anti TNF therapy. CD20 is a calcium channel that can be found on the surface of both normal and malignant B cells. In 2006, the FDA approved rituximab for use in the treatment of RA in combination with methotrexate. In clinical trials, rituximab was demonstrated to be safe and effective in the treatment of RA when coupled with cyclophosphamide or methotrexate. The most prevalent negative effects are reactions at the infusion site. When compared to placebo, Rituximab therapy was not connected to an increased risk of infection, according to studies. It also exhibited no detrimental consequences on IgG levels [9,10].

3.1.5. Inhibitors of Janus activated kinase (JAK): "Janus–Kinase (JAK) Inhibitors" are a brand new family of drugs for the treatment of rheumatoid arthritis. These synthetic DMARDS (ts DMARDS) suppress intracellular tyrosine kinase, making them beneficial in inflammatory diseases. JAKs are essential for signal transduction from the IL-2, -4, -7, -9, -15, and-21 receptors' shared gamma chain to the nucleus. Tyrosine kinase-like receptor-associated intracellular proteins are known as JAKs. They are downstream mediators of several pro-inflammatory cytokines, such as interferons and interleukin 6" [6]. "An intracellular kinase is phosphorylated when a ligand connects to its receptor, causing the signal transducer and activator of transcription (STAT) pathway to be phosphorylated and activated [9]. As a result, blocking these enzymes with a single chemical affects a wide range of inflammatory pathways. Despite the fact that the mitogen activated protein kinase pathway appears to play a role in RA, pharmacological trials targeting it have not generated encouraging outcomes. Medicines that target JAK pathways, however, have

shown promise in the treatment of RA. JAK inhibitors function by preventing the production of cytokines that activate JAK pathways. In RCTs in RA, JAK inhibitors have been demonstrated to be safe and efficacious [6,9].

3.1.6. Biosimilars: Biosimilars are examples of biological products that are highly similar to, but not similar to, reference products and are being studied for independent marketing authorization when the patents on the reference drugs expire [9]. Several biosimilars for RA therapy, including infliximab and etanercept, have either been approved by the FDA or are undergoing clinical trials. Moving from infliximab to the biosimilar CTP13 was found to be acceptable, and therapy may be continued with the biosimilar [9].

3.2. COMBINATIONAL THERAPY IN RA:

Combination therapies Combinations of DMARDs were uncommon in the management of RA prior to the 1990s. Multiple studies have demonstrated the advantages of combined DMARD therapy over monotherapy in managing disease activity and delaying radiographic progression in RA. Most RA combo therapies still include MTX as a key component. Several alternative combination techniques have been successfully used and shown to outperform monotherapy. Triple therapy (MTX, HCQ, and SSZ) and COBRA therapy are two examples of well-established combination regimens (MTX, SSZ, and prednisolone). Many biologic medicines have also been shown to be effective when used in conjunction with MTX. A comprehensive study of individuals with early, active RA found that numerous treatment regimens are successful, but that early combination medications are most effective in reaching clinical remission and enhancing radiographic results. Despite the fact that not all DMARD combinations have been properly examined, it is widely believed that they improve clinical and radiological results. Furthermore, there is a dearth of data on head-to-head comparisons of the efficacy of different therapeutic combinations [14].

3.3 EPIGENETIC THERAPY IN RA:

Heritable changes in the expression of genes that do not impact the nucleotide sequence of DNA are referred to as epigenetic changes [9]. Genetic variation, histone alterations, and microRNA-related genomic regulation are the major mechanisms of epigenetic modifications [9]. Anomalies in these systems have been linked to the beginning of autoimmune disorders like RA in various studies. Understanding of the aberrant epigenetic processes implicated in the pathophysiology of RA has prompted greater study into tissue/cell specific epigenetic clinical markers for early diagnosis and drug development. Medicines that have the power to modify epigenetic marks and restore them to normal levels are known as epigenetic treatments. Commercially available medications include DNMT agents and HDAC inhibitors [9].

3.4. THE POTENTIAL OF MESENCHYMAL STEM CELLS IN RA CELL THERAPY:

Immunomodulatory and tissue-repair properties have been attributed to mesenchymal stem cells (MSCs). The presence of CD90, CD73, and CD105, but not the lack of hematopoietic or endothelial antigens, distinguishes MSCs [9]. MSCs have been obtained from a variety of sources, including bone marrow, adipose tissue, synovium, and the umbilical cord. MSCs are involved in the treatment of inflammation because they have the ability to influence the immune system. “Among other things, CD25+ CD4+ FoxP3+ regulatory T (Treg) cell production is stimulated, and dendritic cell maturation is suppressed” [9]. MSCs control the immune system by interacting directly with cells and creating soluble chemicals like “interleukin 10 (IL-10) and indoleamine 2,3-dioxygenase (IDO)”. In recent research, MSCs have been shown to have immunomodulatory capabilities in inflammatory arthritis by suppressing T cell proliferation and Treg cell function. T cells' ability to contribute to B cells was reduced by human UCMSCs. As a result, MSCs appear to have the ability to reduce inflammation and may be useful in the treatment of RA patients' clinical symptoms [9]

IV. NEW PERSPECTIVES IN THE TREATMENT OF RA:

Significant advancements in RA management over the past few decades have improved the quality of life and results for RA patients. This has been made feasible by the effective identification of multiple pathways implicated in the pathophysiology of RA. However, there are some unmet needs in the treatment of RA as a result of poor understanding of the inflammatory process and the processes underlying the pharmacological effects of therapeutic drugs. Because of their ability to develop into new tissues such as bone and cartilage and their reported in vitro immunosuppressive properties by inhibiting T cell activation, mesenchymal stem cells (MSCs) are also a potential therapeutic approach. Additionally, MSC therapy has been shown to reduce pro-inflammatory responses and improve RA symptoms in both animal model studies and human clinical trials. This is accomplished by reducing blood levels of IL-1, IL-6, IL-8, and TNF-α. The range of available treatments for RA is expanding, and multiple ongoing research have the potential to significantly improve the lives of RA patients by identifying novel molecular targets, therapeutic drugs, and techniques to manage side effects. The future of medicine can be transformed by a personalized approach based on genetic studies combined with evidence-based therapy to successfully treat the untreatable [15].

V. CONCLUSION:

An overview of the therapy strategy for RA was provided in this review, which gathered up-to-date material. Numerous studies exploring various treatments for patients with RA have been conducted recently as interest in managing autoimmune disease has increased. The quality of life for patients has significantly increased, even if the condition is still fatal. Current therapeutic approaches reduce immunological participants and inflammatory mediators in order to either treat symptoms or slow the progression of the disease. Currently, neither of these techniques is curative nor preventative. A tailored approach built on genetic research combined with evidence-based therapy to successfully cure the incurable could revolutionize medical care in the future.

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