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Advancement in the Management of Rheumatoid Arthritis (RA) from Conventional to Recent Trends: A Review

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ABSTRACT

ORIGINAL RESEARCH ARTICLE

The treatment options for rheumatoid arthritis (RA) have greatly increased throughout the last 20 years. New biologics, small molecule drugs, promising agents, and emerging safety signals are all covered in this article. With these new options, remission is within reach, and tapering is a vital part of diabetes therapy on a daily basis. Future studies will provide doctors with the best ways for treating rheumatoid arthritis. Patients' quality of life has greatly improved, even if rheumatoid arthritis cannot be cured. Screening programs, comprehensive information on the disease spectrum, and sickness prevention strategies all have the ability to enhance epidemiological metrics. Making a correct diagnosis quickly is crucial for efficient condition management since symptoms can often be associated with other conditions. Accurate use of ACR-EULAR criteria, detection and quantification of diagnostic biomarkers, and correlation with imaging modalities are three of the many components that go into making a proper diagnosis. The end goal of aggressive pharmacological treatment for rheumatoid arthritis (RA) is to achieve full remission or a significant reduction in symptoms and clinical indicators. Rheumatoid arthritis is now manageable because to research that has improved our understanding of the disease's pathophysiological causes and led to the creation of new therapeutic approaches. Novel biologic medications, such as TNF and IL-1 antagonists, and the early prescription of DMARDs have started to alter rheumatologists' therapeutic approaches. As more data is collected from the use of these agents and other, as-yet-undeveloped agents, rheumatologists will likely make additional adjustments to the way they treat this serious disease, both alone and in conjunction with DMARDs. However, many patients still show little improvement with the current treatments, demonstrating the need for new medications and a greater focus on individualised care.

1. INTRODUCTION

Joints and organs outside of the joints can be affected by the persistent inflammation that characterises rheumatoid arthritis (RA), a systemic inflammatory disease. Arthritis can be either non-inflammatory (osteoarthritis) or inflammatory (from crystal deposition, infections (viral or bacterial) or autoimmune mechanisms) (1, 2). Among the diverse range of conditions are SLE, PM, spondylarthritis, psoriatic arthritis, adult-onset scleroderma, and Sjögren's disease. Because their symptoms are so similar, a differential diagnosis is necessary (3). No one knows for sure what causes RA, but one theory is that the

immune system produces anti-citrullinated protein antibodies (ACPAs) due to dysregulated citrullination (4). The course of RA can be unpredictable, with increasing symptoms and flare-ups occurring even when medication is doing well. A patient's life expectancy can be shortened by a few years due to complications and comorbidities (5, 6). Innovations in the pharmaceutical sector have paved the way for fresh ways of treating rheumatoid arthritis (RA). It is still difficult to comprehend the molecular processes that control the destiny of antibodies (7). For the best results, it's important to catch the problem early, treat it with the right combination of medication and non-medication measures, and check in on its effectiveness and safety periodically. Reduction of adverse effects and attainment of remission are the objectives (8). Maintenance of joint function is achieved by the use of a variety of pharmacological agents, such as synthetic disease-modifying antirheumatic medicines (DMARDs), biologic DMARDs, and targeted synthetic DMARDs. Patients with RA who do not have adequate symptom management often need to be prescribed glucocorticoids and nonsteroidal anti-inflammatory drugs as an additional treatment (9, 10). Multiple variables, including heredity, the environment, and chance, contribute to the complexity of rhumoral artery disease (RA). Approximately half of all cases of rheumatoid arthritis (RA) are hereditary, and there are two subtypes defined by whether or not rheumatoid factor (RF) and anti-cancer proteins (ACPAs) are present: seropositive and seronegative. The PTPN22 risk allele, the HLA-DR allele, and the TRAF1/C5 related genes are the primary genetic variables linked to an ACPA-positive subtype. Interferon regulatory factor 5 (IRF-5) is exclusive to the subtype that lacks ACPA (11). An important part of RA management is addressing environmental risk factors. As a result of the toxic compounds included in tobacco products, smoking is known to transmit a particular signal that can lead to the onset or worsening of RA (12). While smoking has an impact on RA that is beneficial for RF or ACPA, it has little to no effect on RA that is detrimental for ACPA. Those who smoke and have the HLA-DR Beta 1 shared epitope allele are more likely to develop ACPA-positive RA (16). Patients with ACPA-positive RA are more likely to experience the negative effects of occupational silica dust exposure on RA. A uncommon condition of rheumatoid arthritis patients, rheumatoid pneumoconiosis can arise from chronic exposure to silica (14). Studies have also looked at dietary aspects and eating habits, and there is some evidence that vegetarianism, fasting, avoiding red meat, and eating more fruit and fatty fish can reduce the incidence of RA (15, 16).

2. PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS (RA)

In the pre-RA phase, which can last for years before any signs of inflammation in the joints become apparent, immunological activities might take place (Figure 1) (17). During this stage, environmental variables interact with epigenetic changes on the genomic structure to produce altered forms of self-antigens such as vimentin, type 2 collagen, and immunoglobulin G (IgG) (18).

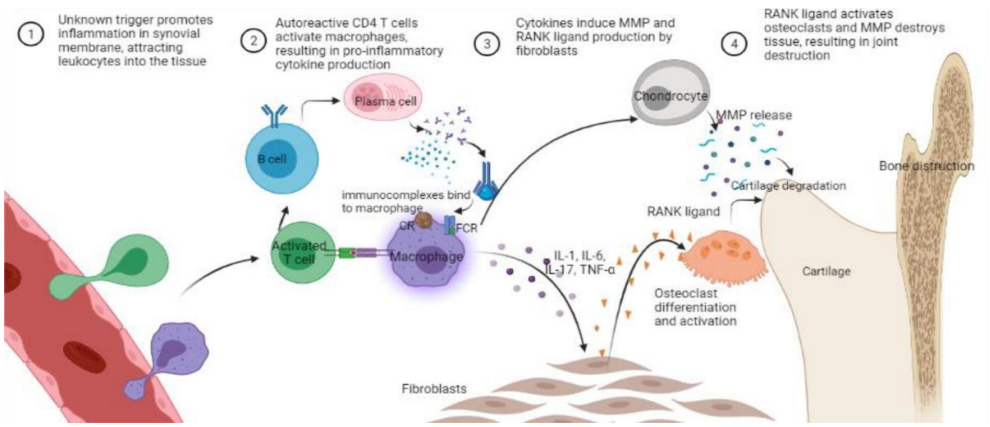

Figure 1: Pathophysiology of Rheumatoid Arthritis (RA)

Citrullination is a post-translational alteration that peptidyl arginine deiminases may perform on proteins that contain arginine residues. Synovial infections and synovial hyperplasia are two examples of joint illnesses that can lead to cytokine release, which in turn can induce inflammation and the development of modified self-antigens (19). Citrullinated proteins are now invisible to the immune system because of the HLA-DR1 and HLA-DR4 susceptibility genes. An immune response is activated when antigen-presenting cells (APCs), which are dendritic cells, take up antigens (20). The lymph node is activated by CD4+ helper T cells once the complex migrates there. B cells in the lymph node's germinal centre undergo immunological activation by co-stimulation, a process involving sequential and reciprocal signals with T cells (21). Autoantibodies are proteins made when the immune system mistakenly targets self-tissues and organs because it can no longer distinguish between self- and non-self components (22). Most research on RA autoantibodies has focused on RF and ACPA, which attach to complement and target the Fc region of IgG (23).

3. MANAGEMENT OF RHEUMATOID ARTHRITIS (RA)

The American College of Rheumatology (ACR) updated its guideline for the treatment of rheumatoid arthritis (RA) in 2021. The update contained 37 recommendations with conditions and seven with strong recommendations about pharmaceutical therapy (Figure 2). Throughout history, several treatment modalities have been employed to improve patients' well-being, decrease the probability of adverse occurrences (EAMs), and gain a deeper comprehension of the safety and efficacy profile of new active molecules (24). In its "Treat to target" initiative, the American College of Rheumatology introduced a new concept. This concept states that in order to attain remission or at least a decrease in disease activity, one must choose an effective therapy (25). There is no turning back the clock on erosions that have already taken place, therefore any treatment must be swift and decisive (26). Preventative measures, nonpharmacological treatments, and pharmaceutical therapies are all part of the standard treatment strategy, which starts with a very precise diagnostic (27).

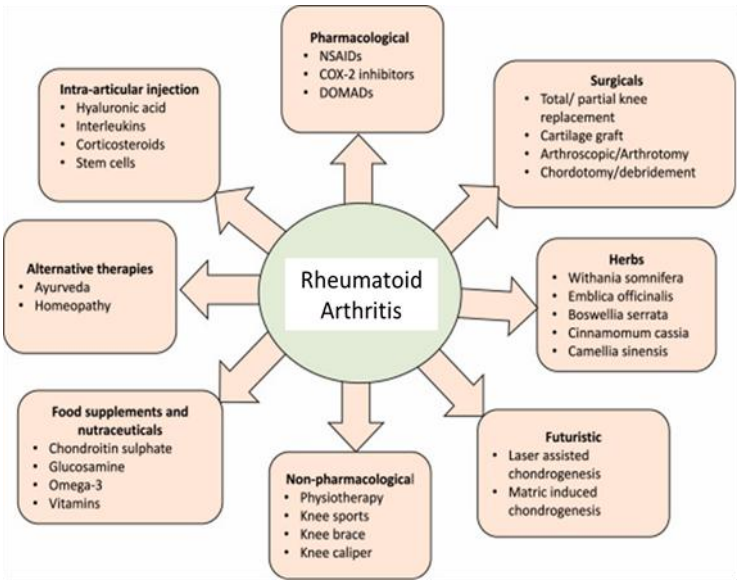

Figure 2: Management of Rheumatoid Arthritis (RA)

3.1 Nonpharmacological Interventions for RA

To get the best possible therapeutic outcome, pharmaceutical therapies should be accompanied by nonpharmacological techniques. There are four tiers of RA management—primary, secondary, tertiary, and clinical—that are aided by the identification of risk factors (28). The goal of primary prevention is to forestall pathological processes; the goal of secondary prevention is to identify and mitigate risk factors; and the goal of

tertiary prevention is to deal with mechanisms that limit harm (29). To reduce complications and halt relapses, clinical prophylaxis is essential. Lower incidence and prevalence rates of RA might be achieved by screening measures for those at risk of getting the disease. Anxiety, melancholy, discomfort, and impaired movement can all be alleviated by nonpharmacological means. The association between polyunsaturated fatty acids (PUFAs) and a number of mental health issues, such as depression and anxiety, has brought them into the spotlight (30). The most effective formulations, according to a meta-analysis of 26 randomised placebo-controlled studies, included at least 60% EPA (31). Omega-3 PUFAs considerably alleviated depression. The possibility that PUFAs might alleviate symptoms of anxiety was also evaluated in another meta-analysis of nineteen clinical studies. Research in the medical field indicates that polyunsaturated fatty acids (PUFAs) may have an effect on the brain mechanisms that cause anxiety, resulting in a marked improvement in symptoms compared to the control group (32). It has been suggested that PUFA supplementation can aid pain alleviation, since a recent prospective study discovered an inverse correlation between patients' pain ratings and DHA blood levels. Anxiety, sadness, and pain are symptoms of rheumatoid arthritis (RA) that are linked to diminished functional capacity and active illness. Although further research is required, PUFAs have the potential to be effective symptom controllers (33). Additional options for RA symptom management include surgery, physical therapy, exercise, occupational therapy, and rest. Only in advanced stages of RA is joint surgery considered, and the rate of occurrence is rare in people younger than 60 years old (34). When looking for alternatives to pharmaceutical painkillers, complementary therapies such massage, posture, temperature therapy, acupuncture, transcutaneous electrical nerve stimulation, and progressive muscle relaxation may be helpful (35). Current RA treatments have a two-pronged approach, treating symptoms (with NSAIDs and GCs) and disease-modifying therapy (with DMARDs), in line with ACR and EULAR guidelines.

3.2 Pharmacological Interventions for RA

3.2.1 Non Steroidal Anti Inflammatory Drugs (NSAIDs)

For pain relief, nonsteroidal anti-inflammatory drugs (NSAIDs) including naproxen, ibuprofen, and coxibs block cyclooxygenase (COX), especially COX-2, which is upregulated during inflammation. Seizures, rashes, disorientation, confusion, bleeding, ulcers of the gastrointestinal tract, renal failure, heart failure, and renal failure are among the major adverse effects that can occur from using these NSAIDs (36). Nonsteroidal anti-inflammatory drugs (NSAIDs) that target COX-2 can alleviate some of the negative effects. Clinical investigations involving RA patients and NSAIDs have demonstrated promising results. Prednisone, hydrocortisone, prednisolone, and dexamethasone are GCs; they have a somewhat better safety profile and more powerful anti-inflammatory and immunosuppressive effects (37). When it comes to rheumatoid arthritis (RA), GCs play a double-duty: first, as a bridge therapy between DMARDs; and second, as an adjuvant therapy for active RA that continues to worsen even after DMARD use (38). Negative feedback in the control of the hypothalamic-pituitary-adrenal (HPA) axis pulsatility makes it imperative not to suddenly quit corticosteroid medication (39).

3.2.2 Disease Modifying Anti-Rheumatic Drugs (DMARDs)

The pharmacological medicines known as disease-modifying antirheumatic drugs (DMARDs) help put joint deterioration on hold and autoimmune activity into remission. These medications take 6 weeks to 6 months to start working. Thirdly, there is the category of targeted synthetic DMARDs, followed by biologic DMARDs, and conventional synthetic DMARDs (csDMARDs) (40). Patients with a fresh RA diagnosis should begin treatment with csDMARDs, and if that doesn't work, they should be prescribed bDMARDs or tsDMARDs. Oral administration is used for tsDMARDs, such as Janus kinase inhibitors (JAKi) (41). The hyperactive immune system is non-targetedly suppressed by csDMARDs, which makes them more often utilised than other treatments with inferior effectiveness and safety profiles (42). Common DMARDs used in rheumatology include

methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide. Drug effectiveness, monitoring needs, cost, and patient characteristics are some of the criteria used to choose a DMARD (43). When further DMARDs have failed to bring the condition under control, MTX is commonly recommended as monotherapy. If this does not work, more DMARDs may be explored for combination therapy as a subsequent course of treatment (44). bDMARDs are a class of genetically modified protein molecules that are categorised according to how they work. Some examples of these groups of drugs are those that block tumour necrosis factor-α, B-cell depleters, B-cell receptors, CD28 antagonists, interleukin-1, interleukin-6, interleukin 12/23, interleukin-17, granulocyte-macrophage colony-stimulating factor, and RANKL. There is a distinct action mechanism for each type (45–47).

3.2.2.1 Leflunomide

Leflunomide, a pyrimidine synthesis inhibitor, is the most recently approved DMARD. It has immunosuppressive and immunomodulatory effects, inhibiting T-cell proliferation, autophosphorylation of epidermal growth factor receptors, and activation of nuclear factor-κB (48). Leflunomide's efficacy was studied in three large phase II clinical trials, showing it significantly increased the proportion of patients experiencing an ACR20 score and improved tender joint counts and swollen joint counts compared to placebo (49). Common adverse events associated with leflunomide include gastrointestinal disorders, alopecia, skin rash, and elevated liver enzymes (50).

3.2.2.2 Sarilumab

A novel biologic for the treatment of rheumatoid arthritis (RA), sarilumab was authorised by the FDA in 2017. This human monoclonal antibody has a stronger affinity for the IL-6 receptor complex than tocilizumab (51) and is directed against the alpha component of that complex. Its structure is unique. Among IL-6's many immune regulatory effects is its activation of the Janus kinase (JAK) signalling inflammatory pathway; this protein is linked to chronic inflammation (52). The soluble IL-6 receptor is more widely distributed, which allows it to cause a greater range of physiologic effects. It has antipyretic, anti-inflammatory, and anti-osteoclast properties, and it can lessen acute phase protein synthesis and bone degradation, which are hallmarks of RA (53). You can take Sarilumab with or without methotrexate for moderate to severe active RA when methotrexate doesn't work well enough or causes intolerance. Dosage should be administered subcutaneously at a rate of 150–200 mg every two weeks. Several phase III trials proved that sarilumab was effective; these trials found that patients responded better to therapy on the American College of Rheumatology (ACR)-20 scale and that sarilumab had comparable benefits for radiographic progression and physical function (54). In a randomised, double-blind, head-to-head study comparing sarilumab with adalimumab, the difference in the change in the 28-joint disease activity score at 24 weeks was statistically significant for sarilumab (55).

3.2.2.3 Etanercept

Etanercept, the first anticytokine medication approved by the FDA for RA treatment, is a dimeric fusion protein and the only TNF-α inhibitor. After 36 months of treatment, it demonstrated long-term efficacy and a favorable safety profile (56). Administered twice weekly via subcutaneous injection, it has a toxicity profile similar to infliximab and has been shown to reduce radiographic progression in RA patients (57). The number of patients who achieved clinical remission with etanercept varied between 50% and 75%. Etanercept-szzs and etanercept-ykro are biosimilars approved by the FDA for RA treatment. Despite a meta-analysis estimating similar efficacy profiles, etanercept had the best drug survival of all TNFi (58).

3.2.2.4 Infliximab

Infliximab is a chimeric monoclonal antibody that neutralizes TNF-α in RA patient, resulting in a decrease in adhesion molecules, IL-1, IL-6, and IL-8. It has a quick response and preventive effect on joint degeneration (59). A cohort study found that switching to infliximab improved efficacy and safety in RA patients with medium and high disease activity, with 37.5% achieving low disease activity and 70.8% achieving moderate or good EULAR response. There was only one serious adverse event identified (60). Infliximab-dyyb, infliximab-abda, infliximab-qbtx, and infliximab-axxq are

biosimilars approved by the FDA for RA treatment. Recent studies show no statistically significant differences in efficacy and safety between bio-original and infliximab biosimilars (61).

3.2.2.5 Certolizumab

Certolizumab is a subcutaneous injection of a human monoclonal antibody, approved for treating RA in pregnant women due to its lack of placental transfer. It is administered every 2 weeks, and biosimilar products are still in the preclinical phase (62).

3.2.2.6 Rituximab

Rituximab, a well-tolerated monoclonal antibody, is not associated with an increased risk of infection, according to a fixed-effect meta analysis. The study found that the risk of serious infection is low even at higher doses. Rituximab is also an effective treatment option for patients with RA who have not responded well to MTX or TNF-α inhibitors (63).

3.2.2.7 Tocilizumab

Tocilizumab is a monoclonal antibody that inhibits IL-6 and is available as an infusion or subcutaneously and intravenously (64). It has a low immunogenicity risk and is more effective than adalimumab monotherapy in reducing symptoms in RA patients with inadequate response to MTX therapy. Common side effects include upper respiratory tract infections, nasopharyngitis, cellulitis, and high blood pressure (65).

3.2.2.8 Abatacept

Abatacept is a fusion protein that blocks T cell activation by blocking CD28 interaction. It is administered intravenous and should be given 2 and 4 weeks after the first infusion, then every 4 weeks. Abatacept has been the subject of numerous phase 3 trials, with a double-blind trial comparing its efficacy and safety compared to infliximab and placebo (66). The study found a similar efficacy profile but a better safety profile for abatacept, with fewer adverse events. However, an observational post-marketing study found that abatacept was only substantially related to an elevated risk of melanoma in RA patients compared to other bDMARDs (67).

3.3 JAK inhibitor (JAKi)

One novel method of treating RA, JAKi, has received approval from both the FDA and the EMA. Proteins located in the cell nucleus known as JAKs mediate the transmission of cytokine signals from receptors on cell membranes to transcription factors known as STATs (68). There are four JAKs and seven STATs that can target them. A significant tool for controlling autoimmune illnesses, JAKi has high effectiveness and safety profiles, is orally administered, and has lower production costs. JAKi has the ability to target four different JAKs family members and seven different STAT kinds (69). U.S. approval was denied to baracitinib in 2017, leaving only the pan-JAK inhibitor tofacitinib on the market. The main goal of the phase III research was the percentage of patients with an ACR20 response at 12 weeks; more patients using 4 mg of baracitinib daily than placebo (70) reached this percentage. The study included 527 individuals with refractory RA. After 24 weeks, 64% of placebo patients and 64% of those taking 2 or 4 mg of baracitinib daily suffered an adverse event. Infections, lower neutrophil counts, and modest increases in low-density lipoproteins with increases in high-density lipoprotein concentration were the adverse events most often reported with baracitinib (71). The safety and tolerability profile of baracitinib stayed the same in a recent open-label extension study, and the drug's effectiveness was preserved throughout the trial (72). Research on the link between RA and COVID-19 has concentrated on the cytokine storm and elevated blood ACPA levels following SARS-CoV-2 infection (73). Epidemiological statistics and progression of SARS-CoV-2 infection are similar to the general population, despite the fact that RA patients are more sensitive due to their autoimmune condition. Immunosuppressive drugs are not associated with the advancement of COVID-19, thus they can be used to treat people who do not have the virus (74). Concerning the problematic topic of RA drug effects on SARS-CoV-2 infected individuals, further study is required. For treatment to be effective, it is necessary to monitor each therapeutic step (75).

4. CONCLUSIONS

A rising interest in treating autoimmune diseases like rheumatoid arthritis (RA) is addressed in this review, which focusses on the disease's management. The last 20 years have seen a dramatic increase in the number of

biologics, small molecule medicines, promising therapies, and new safety signals available for the treatment of RA. Remission is now within reach with these choices, and everyday management is incomplete without tapering techniques. The optimal methods for treating RA will be determined by future trials. Patients' quality of life has greatly improved, even if RA is incurable. Epidemiological parameters can be improved by screening programs, illness preventive methods, and thorough disease monograph information. Effective disease management relies on early and accurate diagnosis, which is made possible by the appropriate use of imaging modalities, diagnostic biomarkers, and ACR-EULAR criteria. Full remission or a marked improvement in symptoms and clinical indications is the end aim of vigorous medication therapy for RA.

5. CONFLICT OF INTEREST: None

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