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Review Paper

Reviewing Advances in Rheumatoid Arthritis Treatment: From Disease-modifying Antirheumatic Drugs to Innovative Drug Delivery Systems

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by inflammatory processes that result in joint swelling, inflammation, and the onset of pain. This discomfort and pathological condition exhibit a gradual rise in scale and become more intense. Even though pharmacotherapy like disease-modifying antirheumatic drugs (DMARDs) and biologics has improved, there is still a need for more focused treatments that cause less harm. This study examines how treatments for RA have changed over time, focusing on the shift from traditional medicines to new, creative ways to combine medicine with immune-engineering therapies. DMARDs are still the most common way to treat RA. On the other hand, biologics and Janus kinase inhibitors are options for people who do not react to their first medications. The development of nanomedicines and hydrogels is an exciting new area of study because they make it possible for more precise spread and less overall toxicity of the medicine. The early research suggests that these innovative approaches could greatly improve the effectiveness of therapy by delivering drugs directly to the site of inflammation while also reducing the severity of any side effects that might occur. RA care is quickly expanding beyond the traditional use of drugs to include more modern ways of managing medications and also personalized healing methods.

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes inflammation in the joints and can also affect other parts of the body. This chronic inflammatory disease often results from a combination of environmental and genetic factors. It especially affects the synovial joints [1]. According to epidemiological data, women are far more likely than men to develop RA, with a lifetime risk of 3.6% for women and 1.7% for men [2]. This disorder usually begins in the small joints on the periphery and progresses symmetrically to affect the proximal joints [3, 4]. If left untreated, RA is a disease that progresses and can lead to higher morbidity and mortality rates [5]. For effective treatment, patients with rheumatoid joint inflammation require a combination of non-pharmacological and pharmaceutical interventions. The current standard of care calls for extremely early treatment with disease-modifying anti-rheumatic medications. Nevertheless, despite therapy, several people continue to suffer from disabilities and significant mortality. Enhancing medical outcomes requires a comprehensive approach that includes individual education and learning, therapy, and physiotherapy [6]. Even though RA treatment has witnessed notable advancements, several issues with current therapy procedures hinder them from working, including systemic adverse effects, ongoing and persistent management routines, and resistance development [7]. By using the molecular pathological environment of RA, immune-engineering therapy can improve therapeutic outcomes and perhaps transform immunotherapy for RA in the future [8]. This article links conventional medical medicines, such as methotrexate (MTX), leflunomide, and sulfasalazine to novel treatments in light of the introduction of disease-modifying antirheumatic drugs (DMARDs) and advancements in drug delivery.

Pathogenesis of RA

Although several risk factors, such as genes, age, gender, obesity, and infections, have been linked to an increased risk of developing RA, the precise origin of the illness is still unknown [9]. Recent studies suggest that RA may be initiated by the interplay between predisposing genes, such as HLA-DRβ1 [10], and environmental factors such as smoking cigarettes [11]. The immune response in RA typically begins in distant sites, including the lungs, gums, and gastrointestinal tract before affecting the synovial joints [1]. These tissues produce changed proteins as a result of biochemical processes, such as citrullination. Environment-triggered RA is caused by the recurrent activation of innate immunity. For example, smoking cigarettes can cause alveolar macrophages in the lungs to express peptidyl arginine deiminase (PAD), which converts arginine to citrulline in the airway [12]. This process generates a neoantigen that triggers an immune response, resulting in the production of anti-citrullinated protein antibodies [12, 13]. While many patients produce autoantibodies, not all of them progress to the actual disease. In some cases, patients may transition from autoimmunity to immune-mediated inflammation concentrated mainly in the synovium [1]. The production of these antibodies is carried out by plasma cells situated in the synovium. RA is characterized by the infiltration of many types of immune cells into the synovium, including innate immune cells (such as monocytes, dendritic cells, and mast cells) and adaptive immune cells (such as T-helper 1, Th1, T-helper 17, Th17), B cells, and plasma cells. In addition, synovial fibroblast-like synovial cells undergo activation [14]. Cytokines and chemokines, such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-monocyte colony-stimulating factors stimulate endothelial cells and recruit immune cells to the synovial region [13]. The fibroblast-like synovial cells in the synovial fluid that is impacted by RA experience a conversion into a more aggressive and infiltrative form. The fibroblast-like synoviocytes, in conjunction with inflammatory cells, produce receptor activators of nuclear factor kappa-B ligand, which initiates the development of osteoclasts, leading to bone erosions, a distinctive feature of RA [15]. Fibroblast-like synoviocytes (FLS) move between joints, resulting in gradual joint deterioration [15]. The involvement of all elements of the immune system is evident, including innate immunity and adapted immunity, which consists of the cellular (T cell) immunological reaction and the humoral (B cell) immune system reaction [16].

RA treatment approach

Continuous improvements in drug discovery processes and procedures have greatly progressed pharmacological approaches in the pursuit of finding a remedy for RA. The most recent therapy options have successfully relieved symptoms, slowed down the evolution of the disease, and prevented any problems. The current treatment approaches, following the guidelines set by the American College of Rheumatology and European Alliance of Associations for Rheumatology tackle RA from two perspectives: Providing relief from symptoms (using nonsteroidal anti-inflammatory drugs [NSAIDs] and glucocorticoids [GCs]) and implementing interventions that affect the course of the illness (using DMARDs) [17, 18].

DMARDs

DMARDs are medicines that hinder the autoimmune process and slow down or reduce joint damage. They are used to bring about recovery. For best effects, therapy should start very early. This is especially true for DMARDs, which take between 6 weeks and 6 months to start working. There are three groups of DMARDs: Conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) [19]. csDMARDs are usually suggested as the first treatment for people who have just been diagnosed with RA. If the first treatment fails to work or is not well accepted, bDMARDs or tsDMARDs should be tried. tsDMARDs can be administrated orally, similar to Janus kinase inhibitors (JAKi) [20].

csDMARDs

csDMARDs are a broad class of pharmaceuticals that include sulfasalazine, MTX, leflunomide, and hydroxychloroquine. Because these medications are safer and more effective than alternatives, such as gold salts, azathioprine, d-penicillamine, cyclosporine, minocycline, and cyclophosphamide, they are frequently recommended. Through their various modalities of action, the overactive immune system is broadly inhibited without focusing on any one feature in particular [4, 21]. As of right now, RA patients who are unable to respond to alternative therapies or who have less severe forms of the disease still require the use of cDMARDs in their treatment (Table 1).

bDMARDs

bDMARDs are a contemporary treatment option for RA that specifically target the immune system's components [21]. bDMARDs are protein molecules that have been genetically modified and are classified into different categories based on their mechanism of action (Table 2).

TNF inhibitors

The first bDMARDs that were approved to treat RA of the joints were the TNF inhibitors. TNF-α is an important cytokine in the development of RA. It has many effects, including induction of the production of other inflammatory cytokines, improving the function of white blood cells, cells that line capillaries, and cells in the synovial membrane layer, blocking the function of regulatory T cells, and stimulating the activation of osteoclasts [25]. There are currently five TNF inhibitors that can be used to treat RA: Infliximab, adalimumab, golimumab, certolizumab pegol plus etanercept. A TNF-receptor structure is what etanercept it while the other options are monoclonal antibodies. On the other hand, certolizumab pegol is a pegylated part of the monoclonal antibody that blocks TNF [26].

Even though they have all been demonstrated to function equally well, bDMARDs that are TNF inhibitors are frequently the first choice for patients who are not responding to MTX. This decision was taken due to the wealth of data, the strategy's shown efficacy, and its well-considered safety and security measures for preventing TNF in the future. TNF inhibitors have been demonstrated by researchers to benefit patients who do not respond well to MTX [26, 27]. However, their effectiveness is further enhanced when used in combination with MTX [28]. Localized injection responses and increased susceptibility to multiple illnesses, including tuberculosis, are the principal side effects of TNF inhibitors. Consequently, regardless of whether a patient has any risk factors for tuberculosis, it is recommended that they should be screened for latent tuberculosis infection before beginning TNF inhibitor therapy [29, 30].

Interleukin-1 (IL-1) inhibitor

Due to elevated levels of IL-1β in the bloodstream and its association with disease severity in patients with RA, it was considered that IL-1β played a key role in the development of RA [31]. Anakinra, a synthetic version of the human IL-1 receptor antagonist, is the sole treatment for RA that specifically acts on IL-1. Anakinra, which received approval from the FDA in 2001, was the initial non-anti-TNF biologic during that period. Recent studies have demonstrated that anakinra exhibits lower efficacy compared to TNF inhibitors [32, 33]. Therefore, due to the availability of more advantageous biologic treatments and the inconvenient requirement of daily subcutaneous injections, this chemical has a limited role in the regular clinical care of patients with RA [34].

Interleukin-6 inhibitors

The IL-6 receptor is inhibited by tocilizumab and sarilumab, and it is essential for the progression of RA. When administered in conjunction with MTX or as a stand-alone treatment for individuals who do not react to MTX, the IL-6 inhibitors have shown efficacy [35] in addition to patients with insufficient response to TNF inhibitors [36]. Head-to-head trials comparing IL-6 inhibitors and TNF inhibitors have shown that IL-6 inhibitors are more effective than TNF inhibitors when administered alone without concurrent csDMARD [37, 38]. Accordingly, these medicines have a role in patients

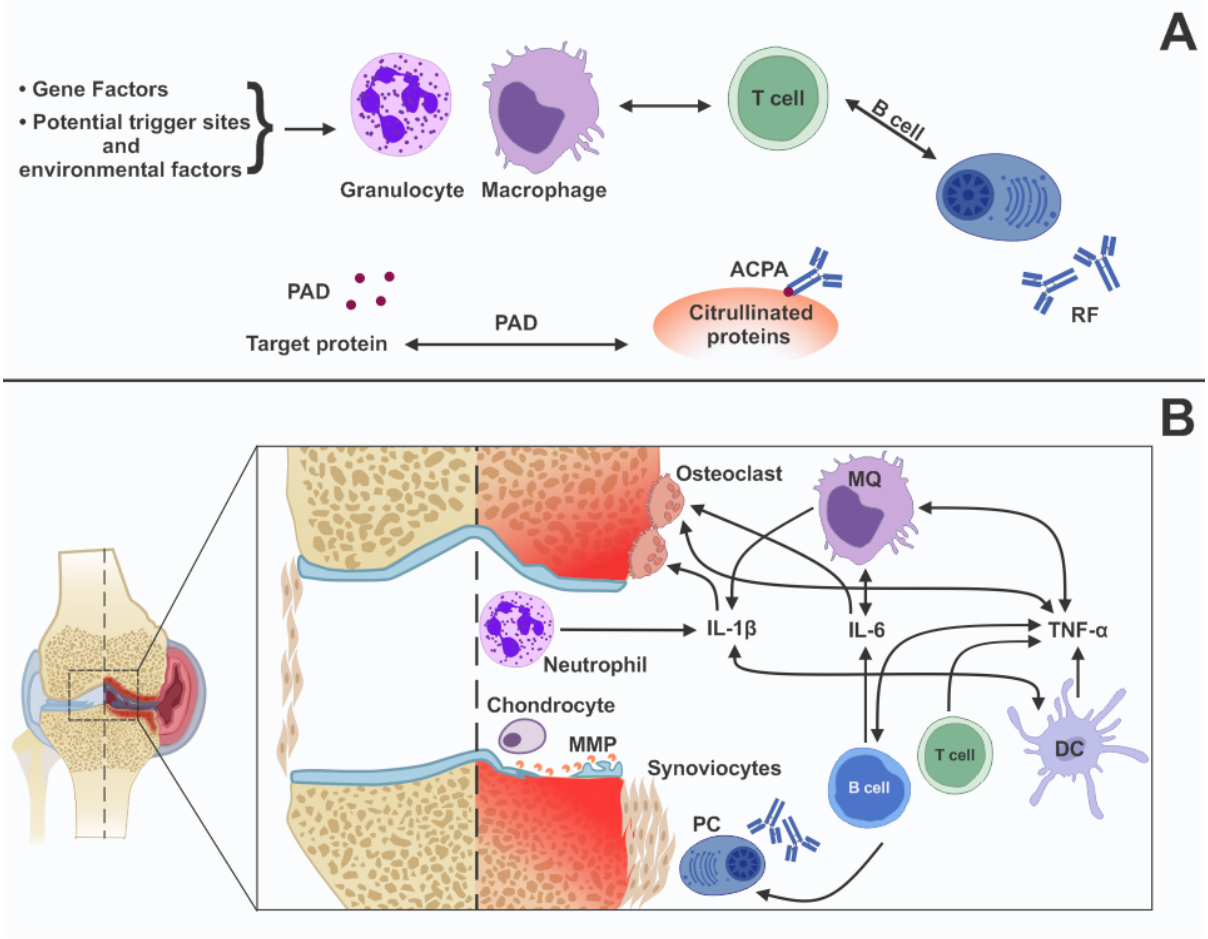

Figure 1. Pathophysiology of rheumatoid arthritis

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Notes: A) RA is linked to various risk factors, including genes. Recent studies suggest that RA may be initiated by predisposing genes and environmental factors. The immune response in RA typically starts in distant sites, including the lungs, gums, and gastrointestinal tract before affecting synovial joints. Environment-triggered RA is caused by the recurrent activation of innate immunity. Smoking cigarettes can cause alveolar macrophages to express PAD, converting arginine to citrulline in the airway. This generates a neoantigen that triggers an immune response, resulting in the production of anti-citrullinated protein antibodies; B) Proinflammatory cytokines, including tumor necrosis factor-α, interleukin-1β, and interleukin-6 are released when B cells, T cells, plasma cells, neutrophils, dendritic cells, and macrophages become activated in RA. These cytokines stimulate osteoclasts and enhance matrix metalloproteinase synthesis, which results in local joint injury. In addition, tumor necrosis factor-α, interleukin-1β, and interleukin-6 seep into the bloodstream, causing systemic inflammation.

who either have a low tolerance or are unable to take csDMARDs. Similar to TNF inhibitors, it is feasible to switch from one IL-6 inhibitor to another when the first one fails. However, it is better to use a different class of medication as an alternative [38].

T-cell co-stimulation inhibitors

Abatacept is authorized for use as either a single therapy or in combination with other non-bDMARDs to treat patients with moderate-to-severely active RA. Unlike other biologics, this is a synthetic protein that combines the extracellular portion of human cytotoxic T-lymphocyte-associated protein 4 with the fragment crystallizable region of human immunoglobulin G1. Abatacept specifically regulates the process of T lymphocyte costimulation by blocking their stimulation through binding to CD80/CD86. This prevents the interaction between CD80/CD86 and CD28 receptors on T cells. Furthermore, it is currently the sole biologic medication available for the treatment of RA that can be administered either subcutaneous injection once a week or intravenous infusion every 4 weeks. According to the findings of the ample research [39], a comparative research was conducted to evaluate the effectiveness and safety of subcutaneous abatacept and adalimumab. The results showed similar efficacy and largely similar safety profiles for both medicines. Abatacept had similar ef-

Table 1. CsDMARDs for rheumatoid arthritis

Drug	Target	Mechanism	References
MTX	Folate-dependent enzymes (DHFR, TS, ATIC)	Reduction of DHFR, TS, and ATIC; impaired synthesis of pyrimidine and purine results in the suppression of lymphocyte proliferation. AICAR rise; elevated adenosine levels exhibit anti-inflammatory properties.	[22]
Sulfasalazine	Folate-dependent enzymes	The mechanism of action is not well understood; however, it inhibits folate-dependent enzymes, similar to MTX. Additional effects are reported as follows: suppression of IκB and initiation of programmed cell death in neutrophils and macrophages.	[23]
Leflunomide	DHODH	Reduction of DHODH; deficiencies in pyrimidine production result in the suppression of lymphocyte growth.	[24]
Aurothiomalate	Broad immunosuppression	Suppression of cellular communication and the display of antigens.	[24]
(Hydroxy) chloroquine	Lysosomes, lysosomal enzymes, TLR-9	It obstructs the process of displaying antigens and hampers the activation of the innate immune system.	[24]

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Abbreviations: AICAR: 5-aminoimidazole-4-carboxamide ribonucleotide; ATIC: 5-aminoimidazole-4-carboxamide ribonucleotide transformylase; DHFR: Dihydrofolate reductase; DHODH: Dehydroorotate dehydrogenase; TLR: Toll-like receptor; TS: Thymidilate synthase.

fectiveness and a favorable safety profile when directly compared to infliximab [40]. Therefore, in addition to TNF inhibitors, abatacept may be a viable choice as the initial treatment for patients with RA who have active symptoms and do not adequately respond to MTX [41].

CD-20 depleting antibodies

A chimeric monoclonal antibody is the kind of antibody that is used to treat rituximab. The elimination of B cells from the body is caused by its particular attachment to the CD20 protein on B lymphocytes. The goal of developing B cell treatment for RA was to reduce the production of deleterious autoantibodies. However, the precise mechanism by which rituximab-induced B cell depletion leads to a decrease in disease progression in RA is not well comprehended. The effectiveness of rituximab is comparable to that of TNF inhibitors, especially in individuals with seropositive RA. Rituximab is equally effective as the first TNF inhibition in individuals with seropositive RA and poor response to csDMARDs [42]. For patients who did not respond well to an earlier TNF inhibitor, switching to rituximab instead of trying a different TNF inhibitor is linked to a better improvement, especially in individuals who test positive for certain antibodies [43]. Nevertheless, the accessibility of this drug as a primary bDMARD is frequently restricted by regional prescribing rules, with numerous countries mandating the preceding ineffectiveness of a TNF inhibitor. Its application is restricted to the management of resistant RA. Rituximab is a favorable therapeutic option for people who have had a past lymphoproliferative malignancy, as it is also effective in treating lymphoma [17].

Antirheumatic drugs approved for the treatment of RA are presented in Table 2.

Biosimilars

bDMARDs are costly, which poses a significant obstacle to their widespread utilization, especially in countries with underdeveloped healthcare systems. Biosimilar medications have been produced as close replicas of their original counterparts. These medications have been demonstrated to possess a similar effectiveness and safety profile as the original bDMARDs. However, their accessibility varies among different nations. Biosimilars of infliximab, adalimumab, etanercept, and rituximab have been created and authorized for the treatment of RA in certain countries. These biosimilars have the potential to decrease healthcare expenses and enhance availability [53]. Several challenges persist in the introduction of biosimilars into the market, notwithstanding the expected dominance of cost constraints. Given the growing accessibility of biosimilars, doctors need to be aware that there is currently limited research on the effects of often switching between different biosimilars, as well as moving back from biosimilars to the original bio-originators [54].

tsDMARDs

One of the most recent treatment approaches approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for RA is the use of JAKi. Based on selectivity, these chemicals can be divided into two groups. The first category consists of weakly selective inhibitors that can prevent a variety of cytokines from signaling. The second group, known as the second generation, can specifically block certain signaling processes. JAKs

Table 2. Approved biological DMARDs for rheumatoid arthritis treatment

Agent	Class	Structure	Target	Mechanism	Approval (US FDA)
Etanercept	Cytokine inhibitor	TNF-α receptor fused with Fc	TNF-α	Binding of decoy receptors to soluble TNF [44]	1998, 1st-line therapy, either alone or in combination with MTX
Adalimumab	Cytokine inhibitor	Human monoclonal antibody	TNF-α	Antibody binding to TNF [45]	2002, 1st-line therapy, either alone or in combination with MTX
Infliximab	Cytokine inhibitor	Murine–human IgG1 chimeric monoclonal antibody	TNF-α	Antibody binding to TNF [46]	1999, the 1st-line therapy was exclusively used in combination with MTX
Golimumab	Cytokine inhibitor	Human monoclonal antibody	TNF-α	Antibody binding to TNF [47]	2009, the 1st-line treatment should only be used in combination with MTX
Certolizumab pegol	Cytokine inhibitor	Pegylated humanized Fab fragment of an anti-TNF-α monoclonal antibody	TNF-α	Fab fragment binding to TNF [48]	2009, 1st-line treatment, monotherapy, or concomitantly with MTX
Anakinra	Cytokine inhibitor	Recombinant IL-1 receptor antagonists derived from human sources	IL-1	Attaching to the IL-1 type-1 receptor [49]	2001, 1st-line treatment, monotherapy, or concomitantly with MTX
Tocilizumab	Cytokine inhibitor	Recombinant humanized monoclonal antibody targeting the IL-6 receptor.	IL-6	Attaching to a soluble IL-6 receptor that is linked to a membrane [50]	2010, the recommended approach was to use this treatment as the initial option, either alone or in combination with MTX
Abatacept	Costimulation blocker	CTLA-4 IgG1 fusion protein	CD80 and CD86	Blocker of T cell costimulation [51]	2005, 1st-line therapy, either alone or in combination with MTX
Rituximab	Cell-depleting agent	Chimeric murine–human monoclonal IgG1k Ab	CD20	Attachment to and depletion of B lymphocytes expressing CD20 [52]	2006, 2nd-line treatment after TNF failure, only in combination with MTX

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Abbreviations: TNF: Tumor necrosis factor; MTX: Methotrexate; IgG1: Immunoglobulin G1; Fc: Fragment crystallizable; Fab: Fragment antigen-binding; IL: Interleukin.

are intracellular proteins that facilitate the transmission of cytokine signals from cell membrane receptors to STAT. This enables precise regulation of the inflammatory response and also presents potential therapeutic applications in the treatment of autoimmune diseases [55]. Furthermore, the JAKs family consists of four members, namely JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Additionally, there are seven types of STATs, namely STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, which can serve as targets for JAKi [56]. Furthermore, JAKi provides notable benefits, such as high effectiveness and safety, as well as the convenience of oral administration. Additionally, JAKi has the advantage of reduced production costs compared to bDMARDs [57, 58].

Tofacitinib is the initial JAK inhibitor that was developed and made available for commercial use specifically for treating RA [59]. Xeljanz was granted approval by the FDA in November 2012 and thereafter introduced on the market. The first target population consisted of persons diagnosed with RA who experience moderate to severe symptoms and have not responded well to, or cannot tolerate MTX treatment. Tofacitinib received approval from the EMA in March 2017 following more than 4 years of aftermarket safety surveillance in North America [59].

The JAK pathway has garnered more attention in the pharmaceutical sector, leading to the creation of baricitinib (oluminant) by Eli Lilly and upadacitinib (rinvoq) by AbbVie. These drugs received the FDA approval in May 2018 and August 2019, respectively. Each JAK inhibitor has distinct therapeutic targets, leading to some notable distinctions. Tofacitinib is a potent inhibitor of the JAK family, specifically targeting JAK1 and JAK3 while having minimal effects on JAK2 and TYK2. Baricitinib is a drug that inhibits the activity of JAK1 and JAK2 enzymes. It also has some effect on the TYK2 enzyme, but very little effect on the JAK3 enzyme [60, 61]. Upadacitinib specifically targets the JAK1 pathway. The reasoning behind this is that a more targeted selectivity of JAK inhibition could decrease the toxicity and side effects associated with higher doses, while still maintaining a similar level of effectiveness [55].

Recommendation

Patients with a severe active infection should temporarily stop DMARD medication, which includes biologic medicines and targeted synthetic drugs like tofacitinib. They can be continued once the infection has been resolved and antibiotic therapy has been finished. All patients initiating therapy for RA must undergo screening for hepatitis B and C as well as tuberculosis. Patients with liver illness should refrain from using MTX. Before starting biologic and targeted synthetic medicines, patients with latent tuberculosis must finish their treat-

ment for a minimum of one month. If patients are unable to tolerate or finish the treatment of latent tuberculosis, it is recommended to undergo conventional DMARD therapy. Patients with pre-existing skin cancer and lymphoproliferative conditions should refrain from using biologic medicines, except for rituximab for patients specifically diagnosed with lymphoproliferative disorders. This is because data indicates that B-cell suppression with rituximab treatment can be beneficial in such circumstances. Before initiating therapy for RA, the American College of Rheumatology advises that patients should get vaccinated for pneumococcus, hepatitis, influenza, human papillomavirus, herpes zoster virus, and COVID-19 [62].

Immuno-engineering

Given the constraints posed by transport obstacles, immunogenicity, and targeting effectiveness, it is imperative to employ immuno-engineering techniques to enhance delivery efficiency and minimize toxicity when utilizing standard cDMARDs (such as biomacromolecule medicines and cells). Immuno-engineering encompasses the creation and advancement of nanotechnology and biomaterials that interact with the immune system. This is accomplished by using a systematic strategy founded in immunological principles, leading to a wide range of possible treatments for RA. The strategy is based on the selective targeting of important immune cell pathways by immuno-engineering approaches, thereby making use of biological reactions to facilitate immunotherapy [63]. Present immunomodulatory strategies are based on three approaches: 1) Administering autologous or allogenic cells from an external source; 2) Using genetic engineering or gene therapy to modify both resident and external cell populations; 3) Utilizing biomaterial-based systems that function as immunomodulators and assist in delivering cells or materials for genetic engineering of resident cell populations. Although individual tactics can be employed alone, immuno-engineering often integrates multiple approaches to create treatments that are more regulated and precise [8].

Nanotechnology for RA treatment

Immuno-engineering therapy shows promise in the field of nanotechnology by targeting specific immune cells or organs. MTX, a folate antagonist, is the most often utilized small molecule medicine for treating RA. It works by inhibiting the growth of immune cells [64]. However, MTX shows poor absorption and can cause negative effects such as myelosuppression and hepatotoxicity [65]. By utilizing the enhanced permeability and retention effect, nanotechnology can improve the pharmacokinetics of MTX while simultaneously decreasing its toxicity by the encapsulation of MTX in polymeric nanoparticles or liposomes [66]. Biomaterials can be altered by nanotechnology by adding targeting agents, including peptides, antibodies, or tiny molecules. The purpose of this modification is to protect these biomaterials from deterioration, limit unwanted effects, and boost their concentration in certain tissues. As a result, immunotherapy can become substantially more effective [67]. Researchers have currently looked at a variety of nanomedicine delivery technologies, including liposomes, micelles, and nanoparticles, to transfer diverse kinds of cargo, such as biologics, nucleic acids, and small-molecule medications. By increasing targeting effectiveness, lowering dosage, and minimizing side effects of conventional drugs, these systems seek to improve the efficacy of immunotherapy for RA [67].

Liposomes and exosomes

Phospholipids are arranged in two layers to form small, spherical structures called liposomes. They can contain materials that have varying solubility properties, like molecules that are hydrophobic, amphipathic, or hydrophilic. Recent studies have shown that liposomes can effectively reduce arthritis by increasing medication accumulation and decreasing the expression of cytokines that cause inflammation [68, 69]. Ren et al. [70] proposed that modifying the size, external charges, and polyethyleneglycol length of liposomes might greatly improve the effectiveness of targeted dexamethasone therapy. The findings indicate that liposomes have the potential to enhance the accumulation of dexamethasone within inflammatory joints, where it is absorbed by fibroblasts and macrophages. In addition to MTX, liposomes can also be utilized as a delivery system for catalase in RA therapy. Chen et al. [71] demonstrated that liposomes composed of 1-palmitoyl-2-oleoylphosphatidylcholine, FOL-S100, and cholesterol can target activated macrophages and break down hydrogen peroxide into oxygen and water. This ultimately enhances the therapeutic effectiveness of MTX. GCs and tofacitinib are commonly administered medications using liposomes as a delivery system [72, 73]. Exosomes have demonstrated a strong inclination to provide anti-inflammatory and tissue-repairing effects that are comparable to those of their parent cells, such as MSCs and macrophages. Additionally, it regulates symptoms of RA by releasing micro RNAs, proteins, and catalysts to decrease the influx of immune cells into the affected joint of RA patients [74, 75]. Zhang et al. [76] described a modified form of exosomes produced from neutrophils, which were modified with ultrasmall Prussian blue nanoparticles using click

chemistry. This modified exosome was found to activate fibroblast-like synoviocytes and minimize inflammatory events by modulating the TH17/Treg signaling pathway, leading to improved joint health.

Nanoparticles

Nanoparticles are minute particles with sizes ranging from 1 to 100 nm, and they can be composed of metals, polymers, lipids, and proteins. These characteristics render them highly valuable for a diverse array of uses in the treatment of RA [77, 78]. Lyu et al. [79] integrated MTX into mannose-modified MTX-M-NP nanoparticles to specifically target neutrophils with the medicine. The results indicated that MTX-M-NPs have the potential to decrease the levels of inflammatory cytokines and prevent bone deterioration in individuals with RA. B cells play a crucial role in both the immune system's response and the development of RA [79]. Wu et al. [80] proposed a therapy strategy for RA, including the use of nanoparticles to transport small interfering RNA (siRNA) called siBAFF. The purpose of this approach is to specifically target the BAFF receptor in B cells. It has the potential to reduce the number of B lymphocytes within the joint, hence inhibiting inflammatory activities. The method may also decrease levels of anti-collagen immunoglobulin G (IgG) in the blood, while simultaneously enhancing the expression of collagen type II and osteocalcin in joint tissues that have been dissected. Jhun et al. [81] explained the use of hybrid nanoparticles made up of liposomes and gold, which are loaded with CoQ10 (LGNP-CoQ10). These nanoparticles are designed to specifically target the STAT3/TH17 pathway, which plays a role in the inflammatory response. These findings indicate that LGNP-CoQ10 is effective for treating RA.

Researchers have looked into using stable metal-organic framework viruses as active nanoparticles for RA immuno-engineering therapy in addition to traditional nanoparticles [82]. Li et al. [83] created prodrug nanoparticles based on chondroitin sulfate that could carry retinoic acid and the photosensitizer chlorin e6. This delivery method blocks the Golgi apparatus and prevents the synthesis of immunosuppressive cytokines to lessen the immunosuppressive effects of photodynamic therapy.

Microspheres and micelles

Because they may be made especially to contain medications or other bioactive chemicals for targeted distribution into RA tissues, microspheres and micelles have found widespread use in medication delivery. While micelles are amphiphilic molecules, such as lipids or surfactants, that can spontaneously organize themselves in water as emulsifiers to dissolve drugs or substances that are not readily soluble, microspheres are often solid or hollow spheres [84]. Bassin et al. [85] created a small spherical particle (TRI-MP) using a combination of polylactic-co-glycolic acid and mPEG. This particle is designed to transport ransforming growth factor β (TGF-β), rapamycin, and IL-2 (TRI). The findings showed that the administration of TRI-MP through intra-articular injection successfully decreased the occurrence of arthritis, reduced the severity of arthritis scores, and prevented bone degradation. These results indicate that TRI microparticles could be a promising treatment choice for RA. Wang et al. [86] created a micelle system using PCL-PEG to enhance the effectiveness of low-dose glucocorticoid treatment. The micelles can encapsulate dexamethasone and specifically target inflammatory joints. The findings demonstrated that the micelles were able to significantly decrease the expression of inflammatory cytokines in individuals with RA. Xu et al. [87] described it as a micelle composed of octadecanoic acid-grafted dextran and sialic acid. The micelles can encapsulate MTX, resulting in a considerable inhibition of the inflammatory response and a reduction in the negative effects of MTX. Additionally, researchers indicate that micelles may improve bone regeneration and repair by stimulating the differentiation and mineralization of osteoblasts. The application of nanotechnology to enhance the delivery of medications for RA is a captivating development [88]. Nanocarriers, including liposomes, nanoparticles, and micelles, might improve the efficacy of DMARDs by enabling precise drug release and minimizing the risk of toxicity throughout the body. The concept of simultaneously addressing numerous pathways in the intricate mechanism of RA using nanomedicines has great potential. By creating nanocarriers that can deliver drugs to specific joints and maximize therapeutic efficacy while reducing side effects and dosage, researchers can potentially improve treatment outcomes [89]. The topic of nanomedicine for RA holds great promise for improving patient outcomes and quality of life through ongoing research and improvements. It is beneficial to see how these technologies develop and affect the management of this chronic autoimmune illness in the future [89].

Hydrogel biomaterials for RA

Hydrogels are crosslinked, three-dimensional networks of hydrophilic polymers with the ability to absorb a lot of water without losing their structural integ-

rity [90]. Collagen, hyaluronic acid (HA), and PEG are examples of manufactured and natural polymers that can be combined to create hydrogels. Scaffold materials used in tissue engineering have several qualities that contribute to their attractiveness, such as significant water content, biocompatibility, and the capacity to imitate the extracellular matrix of natural tissue [91]. Hydrogels possess a range of characteristics, such as robustness, rate of breakdown, and ability to interact with living organisms, which allow them to imitate the microenvironment of tissues [92], facilitating cellular growth, replication, and specialization. These attributes render them a compelling choice for immuno-engineering applications in RA [93].

Hydrogels can contain NSAIDs and DMARDs and transport them directly to joints, which reduces the harmful effects on the entire body and enhances the effectiveness of the drugs at specific locations. Additionally, hydrogels can also carry growth factors or other bioactive substances that stimulate cell growth and differentiation, while regulating the immune response [94]. Seo et al. [95] presented findings on the effectiveness of a click-crosslinked HA depot for injection in extending the therapeutic effects of RA treatment in the joints. The findings indicated that HA can create a durable and flexible hydrogel upon injection, allowing for continuous release of the loaded MTX. The synthesized MTX-Cx-HA hydrogel has the potential to enhance articular index scores, augment cartilage thickness, promote the growth of chondrocytes and glycosaminoglycan deposits, and inhibit the expression of TNF-α and IL-6. Joshi et al. [96] created a hydrogel system for medication delivery using TG-18, which can spontaneously assemble into hydrogels that respond to arthritic flares. According to their findings, the platform can administer triamcinolone acetonide (TA) and demonstrate sustainable drug release properties to decrease arthritic activity. Hence, the use of injectable hydrogel shows potential as a viable method to extend the duration of therapeutic effects in the treatment of RA. Ma et al. [97] created a hydrogel called GDFDFDY that self-assembles at the supramolecular level. By incorporating MTX into the hydrogel, we formed MTX-GDFDFDY hydrogels. These hydrogels effectively reduced symptoms of joint swelling in RA and protected cartilage. Our findings suggest that MTX-GDFDFDY hydrogels have the potential to be used as a therapeutic approach for RA. Zhao et al. [98] have created a versatile liposome hydrogel (DS-FLs/DEX) by combining dextran sulfate (DS) and DEX by transdermal formation. The findings indicate that DS-FLs/DEX exhibited prolonged drug release and effectively infiltrated and accumulated in inflamed joints to reduce inflammation and mitigate the negative impact of RA on bone, demonstrating its efficacy as a promising drug delivery system for RA treatment.

Hydrogels have become a viable approach for tissue engineering in RA. They may be customized to display various characteristics and have been used in preclinical investigations for medication delivery, cell delivery, and scaffold materials. Hydrogels possess significant potential for the advancement of efficient treatments for RA while minimizing the occurrence of adverse effects. Even though hydrogels have promise for RA immunoengineering, several limitations to their application need to be recognized and addressed. One major challenge is that hydrogels do not have long-term stability in living beings since the immune system can quickly break them down or remove them. Moreover, the complex synovial joint milieu, which includes a variety of immune cells and cytokines, makes it challenging to create hydrogels that effectively control the immune response [99].

Conclusion

A wealth of research on the treatment of RA points to a dynamic area in which both biologic and non-biologic traditional DMARDs remain essential for controlling the condition. The therapeutic landscape has expanded with the introduction of biosimilars and JAKi, providing patients with new options that may be more affordable while maintaining equivalent efficacy. In these developments, immuno-engineering appears as a promising area for future research, utilizing hydrogels, biomaterials, and nanotechnology to directly address the intricate workings of the immune system. These innovative methods offer more patient-specific therapy options, fewer side effects, and improved medication administration. Nevertheless, despite the excitement about novel treatments, more investigation, testing, and refinement are necessary to overcome the current problems with medication administration, long-term effectiveness, and security. To fully grasp the potential of these developing medicines in the fight against RA, researchers, doctors, and patients must work together in a concerted effort. The development of next-generation RA therapeutics is promising given the advancements in immuno-engineering and nanotechnology. To completely achieve the therapeutic potential of these techniques, more research is needed to determine their effectiveness, safety, and long-term results.

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Compliance with ethical guidelines

There were no ethical considerations to be consideredin this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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