

Research progress in the treatment of rheumatoid arthritis

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Abstract

Rheumatoid arthritis RA is a systemic immune inflammation of unknown etiology, which mainly damages the synovium of the joints, leading to joint deformities and loss of function. Its drug treatment currently includes traditional anti-rheumatic drugs, biological agents and various biosimilars. Biological agents have shown obvious advantages in recent years and have been widely used. In recent years, there have been many research related to new treatment methods, such as: microbial therapy, tuned cationic dendrimer therapy, etc. This article focuses on the review of new developments in rheumatoid arthritis treatment drugs and methods.

Keywords: Rheumatoid Arthritis, Drug Therapy, Treatment Progress.

Introduction

Rheumatoid arthritis RA is a systemic autoimmune disease characterized by joint pain, swelling and progressive erosion. Reduced quality of life and even death [1]. Studies have shown that a variety of factors work together to lead to the development of RA, such as smoking, obesity, gut microbiota, infection and genetic factors. The etiology has not been fully elucidated [2,3]. As a chronic progressive disease, RA has no cure at present. The combination of non-steroidal anti-inflammatory drugs and anti-rheumatic drugs has become the cornerstone of treatment. It can reduce the activity of the disease and delay the disease process. However, some patients still cannot tolerate it. Or the condition cannot be satisfactorily controlled [4]. In recent years, with the in-depth research on the pathogenesis of RA, new drugs for the treatment of RA have been continuously developed. At present, there are many new treatment methods being researched, and the latest progress will be elaborated in turn.

Drug Treatment

Traditional Antirheumatic Drugs

Traditional anti-rheumatic drugs are still the basic drugs for RA treatment, often combined with other anti-rheumatic drugs, especially methotrexate, leflunomide and glucocorticoids [5], and a lot of research The efficacy of their combination therapy has been demonstrated, but the clinical use of these drugs is limited due to their obvious adverse effects.

Biologics: Biologics, also known as biological anti-rheumatic drugs, are a more direct, clear, and targeted treatment than traditional anti-rheumatic drugs, which can delay the progression of RA disease, but because of their serious adverse effects Limited, such as increased risk of infection, leading to neurological diseases such as multiple sclerosis and lymphoma [6]. Currently available biologics include tumor necrosis factor inhibitors TNFi, IL-1 receptor antagonists, IL-6 receptor antagonists, B cell depleting agents, T cell targeting drugs, SYK inhibitors and JAK kinases Inhibitors, which belong to different drug classes, have different pathophysiological targets [7].

TNFi: Tumor necrosis factor TNF, a messenger protein that promotes joint inflammation, has multiple cellular effects. TNF- α is produced by activated monocytes, macrophages and T lymphocytes and exerts pro-inflammatory effects through TNF receptors 1 and 2. The interaction of TNF- α and its receptors can activate key signaling pathways, such as NF- κ B pathway, RANKL signaling pathway, extracellular signal-regulated kinase signaling pathway, tumor progression site 2 pathway, and pro-apoptotic pathway, etc. [8]. TNFi such as etanercept, rituximab, adalimumab, golimumab, and certolizumab all provide rapid symptom relief by preventing inflammatory cell aggregation [9]. Studies have shown that TNFi can reduce the risk of myocardial infarction in patients with RA compared with other biological agents [10].

IL-1 receptor antagonists: IL-1 is a cytokine with immune and pro-

inflammatory effects, and there are two specific immunoglobulin-like membrane-bound IL-1 receptors IL-1R, IL-1RI and IL-1RII. On the cell surface, in contrast to IL-1R I, IL-1R II does not transmit signals, but acts as a decoy receptor that binds and inhibits IL-1 [11]. Anakinra is an aglycosylated, recombinant form of an IL-1 receptor antagonist that differs from native human proteins by having an additional N-terminal methionine that reduces IL-1 binding to the IL-1 receptor α and IL-1 β activity; it can be used as a monotherapy or in combination with rheumatic drugs, but should not be combined with TNFi; adverse effects include gastrointestinal reactions and allergies and upper respiratory tract infections. Studies have found that anakinra can improve cardiac contractility [12]. Therefore, anakinra is a better choice for patients with severe or refractory pericardial disease and/or heart failure.

IL-6 receptor antagonists: IL-6 receptor antagonist is an important receptor blocker, and blocking the IL-6 signaling pathway plays a key role in maintaining RA therapy. IL-6 levels are elevated in serum and synovial fluid in RA patients. IL-6 has multiple roles in the inflammatory process, such as stimulating plasma cells to produce autoantibodies, participating in the differentiation of T helper cells to Th17 cells, stimulating osteoclastogenesis, and promoting the formation of pannus and pannus in inflammatory joint tissues. Proliferation, destruction of affected joints, resulting in extra-articular manifestations [13]. IL-6 antagonists can effectively reduce the production of acute phase protein, play an antipyretic effect, inhibit the formation of osteoclasts, and reduce the bone destruction of RA.

B cell depleting agents: B lymphocytes may be involved in the initiation and maintenance of inflammatory cascades through their effects on antigen expression and production of various pro-inflammatory cytokines. Rituximab is a genetically engineered chimeric monoclonal antibody that binds to CD20 to deplete B lymphocyte subsets through cell-mediated, apoptosis-promoting, and growth-arresting pathways [14]. Rituximab is mainly used to treat TNFi-resistant RA patients, especially those with vasculitis and cryoglobulinemia.

T cell targeted drugs: The inflammatory response in RA is driven by T cells, especially CD4+ T cells, which are the dominant cell type 30% to 50% of all cell types in the synovium of RA patients. T cell infiltration into synovial joints increases the levels of pro-inflammatory cytokines such as interferon- γ and IL-17, causing synovial cartilage and bone destruction [15]. Abatacept, a biopharmaceutical that acts by blocking T cell activation, is a T cell costimulatory modulator and a fully human soluble fusion protein [16], which consists of the extracellular domain of human CTLA-4, Human IgG1-modified Fc moieties are attached, which do not directly inhibit inflammatory proteins, but prevent these cells from binding to each other by attaching to their surfaces.

Janus Kinase JAK Inhibitors: JAK kinase inhibitors are small-molecule biologically targeted therapeutics that inhibit components of the intracellular inflammatory signaling cascade.

JAK kinases are essential components of various intracellular signaling pathways involved in the pathogenesis of RA, they bind to the cytoplasmic domain of cytokine receptors and are activated upon binding of cytokines to their cellular receptors [17]. The JAK family of enzymes consists of four members, JAK1, JAK2, JAK3, and TYK1, which play important roles in host defense, hematopoiesis, body growth, neural development, and immune responses. JAK enzyme inhibitors act on RA by blocking intracellular JAK. Tofacitinib and baricitinib are the first oral JAK small-molecule inhibitors available for the treatment of RA, which can rapidly relieve RA symptoms, delay disease activity, and improve its prognosis.

Syk inhibitors: Syk is a non-receptor tyrosine kinase widely expressed on hematopoietic cells, lymphocytes, fibroblasts, and vascular endothelial cells, and is the most important kinase in the process of B cell activation signal transduction [18]. important role in the mechanism. Syk inhibitors work by blocking the Syk signaling pathway, thereby suppressing the inflammatory response, and Fostamatinib is one of them.

Biosimilars

Biosimilars are an important new class of drugs in rheumatoid medicine. Due to the complex molecular structure of biologics, imitation of these drugs is impossible, so regulatory agencies define them as “no clinical significance with existing FDA-approved reference products.” “Differential” products are subject to rigorous pharmacokinetic and pharmacodynamic testing and immunogenicity assessment. In the past 20 years, biologics have greatly improved the treatment of RA patients. The recent development of biosimilars, if available at lower cost, could increase access to these treatments and increase the number of patients who benefit from such treatments [19]. Two biologics based on the monoclonal antibody infliximab are currently approved for the treatment of RA in the United States, with CT-P13 Inflectra being the first. A biosimilar of etanercept, SB4 Benepali, has been approved in Europe [20].

Surgical Treatment

Synovectomy

The purpose of synovectomy surgery is to remove hypertrophic, inflammatory diseased synovial tissue within the joint and to prevent or slow further joint destruction. More than 70% of patients with joint swelling are caused by synovial tissue lesions [21]. For patients who still have joint pain and swelling after conservative treatment for 3 to 6 months, and have imaging changes, synovectomy should be performed.

Arthrodesis: When RA progresses further and the patient experiences significant joint pain, which seriously affects the quality of life, and is accompanied by joint instability, arthrodesis should be considered. The fused joint, although the range of motion is lost, is more functional in daily life than a joint that is mobile and painful, especially when the wrist, metacarpophalangeal, interphalangeal, ankle, or foot joints After arthrodesis of each joint

of the upper part, the loss of joint function can be well compensated by the adjacent joint [22].

Artificial joint replacement: After the joint deformity of the upper extremity in RA patients, the wrist deformity should generally be corrected before hand surgery to restore the upper limb alignment. However, whether the deformity needs to be corrected first during shoulder and elbow surgery is still debated [23]. In the lower extremities, before hip and knee replacement surgery, foot and ankle surgery should be performed to provide conditions for recovery after joint replacement. Ipsilateral hip replacement surgery should usually be performed before repairing and reconstructing the knee, but if knee deformity and pain are severe, it can be corrected first.

The Latest Research Progress Stem Cell Transplantation Therapy

Traditional anti-rheumatic drugs have serious side effects. Although biological agents are widely used in clinical practice and have positive effects, their economic costs and immunosuppression greatly increase the risk of various infections and tumors in the body, and they cannot repair the bone destruction of RA. Mesenchymal stem cells MSCs have great therapeutic potential as a novel therapeutic option for the treatment of rheumatic diseases [24]. MSCs are pluripotent cells with abundant sources and can be isolated from adult tissues such as bone marrow, adipose tissue, placenta or umbilical cord. Recent studies have found that synovial MSCs have high chondrogenic capacity and can be a candidate cell source for cartilage and meniscus regenerative medicine. MSCs have self-renewal ability and multi-directional differentiation potential, and can differentiate into osteoblasts, chondrocytes, adipocytes, etc. under specific conditions. Bone destruction provides a theoretical basis. MSCs express MHC class I molecules on the surface, but do not express MHC II, Fas ligand and costimulatory molecules CD86, CD80, etc., so they are not recognized by T cells and can escape immune surveillance. In the study of MSCs in the treatment of RA, it was found that MSCs reduced the content of pro-inflammatory factors Th17, TNF- α , IL-6, B cells and increased the content of anti-inflammatory factors IL-4, IL-10 by up-regulating the proportion of Treg cells. To reduce local cartilage destruction and bone erosion in joints, the potential of MSCs as a treatment option for RA is demonstrated. Foreign clinical trials on MSCs in the treatment of RA have shown that stem cell transplantation can reduce the levels of HAQ, DAS28 [25], C-reactive protein and rheumatoid factor, increase the proportion of Treg cells, and quickly relieve joint pain and swelling. The overall safety is better. Good, less adverse reactions.

Microbial Therapy

Recent evidence suggests that the gut microbiota directly or indirectly modulates the host's immune system. RA has been associated with gut dysbiosis. Combination of DMARDs in RA-treated patients showed partial recovery of the eugenic gut microbiome. Therefore, understanding the impact of DMARDs on the microbial composition and its consequences could identify novel therapies for RA on the host immune system. Microbiome

and rheumatoid arthritis microbial colonization occurs before birth and continues to change and diversify until stable at approximately 3 years of age. Gut microbes can bind nod-like receptors and toll-like receptors TLRs to activate the immune system [26], as well as produce metabolites called short-chain fatty acids SCFAs that can interact directly with the host. Maintaining a well-balanced microbiota contributes to maintaining a state of tolerance within the gastrointestinal tract by interacting with the gut to generate immune-reactive epithelial cells. To date, studies have shown that the gut microbiome has a profound link with host immunity. First report establishing a link between microbiota and pathology. DMARDs are widely used to treat RA. In addition to DMARDs, which have immunomodulatory properties, they can also modulate the host microbiome. Studies point to gut dysbiosis. In RA patients, interestingly, studies have shown that the subjects' adverse biological microbiome has partially returned to normal or has been altered to increase beneficial microbes. The number of members who received MTX and HCQ was associated with disease activity [27]. There are limited reports on the effects of chloroquine, SSZ and other drugs on the gut microbiome. Since these drugs have antibiotic properties, they can be predicted to have a direct modulating effect on the gut microbiota. According to the data available in RA and arthritis animal models, the key role of altered gut microbiota in patients lies in disease severity. Since recovery after partial microbial therapy is associated with therapeutic efficacy, drug-microbiome network associations may provide an effective strategy for the future treatment of RA. However, disease heterogeneity and variability in treatment must be considered. Given that the gut microbiome is influenced by genetic and environmental factors, it is conceivable that for probiotics, one size fits all may not apply. There is growing interest among patients to use alternative or adjunctive treatments, such as herbal remedies or probiotics. Currently, more work needs to be done regarding drug-microbiome interactions and limited RA with probiotics [28], which can be used for immune homeostasis. It may also contribute to personalized medicine where the enrichment of probiotic commensal/low metabolism in patients can be complemented to generate immune homeostasis.

Novel Molecular Therapy

Free deoxyribonucleic acid cfDNA released after cell death or damaged cells serves as a key autoantigen RA in rheumatoid arthritis [29]. They can be recognized by nucleic acids NA, such as toll-like receptor sensors TLRs, leading to activation of the innate immune system and chronic inflammation. Cationic molecules were screened by cationic dendrimers as scavengers that could eliminate cfDNA and inhibit TLR recognition and nucleic acid-induced inflammation. This structure and property study demonstrates that toxicity, NA-binding capacity and biodistribution can be balanced by refined control of molecular structure for maximal therapeutic effect. Furthermore, the optimized cationic polymer effectively suppressed joint swelling [30], synovial fluid hyperplasia and bone destruction in a collagen-induced arthritis CIA rat model. Supporting results identified synthetic polymers offer novel treatments for autoimmune diseases.

Discussion

To sum up, the etiological treatment of RA is still difficult. Traditional anti-rheumatic drugs are used as the basic drugs in the treatment of RA, and are often used in combination with biological agents. TNFi in biological agents is fast and effective in the treatment of RA, and can also inhibit the progress of structural joint damage. IL-1 antagonists are a good choice for RA cases with severe or refractory pericardial disease and/or heart failure, IL-6 inhibitors and B cell depleting agents can be used in cases where TNFi is ineffective; targeted synthetic anti-rheumatic Drugs are effective for refractory RA. If biosimilars are low-cost and can obtain the same pharmacological effects as biologics, more RA patients will benefit. Biological agents and their generic drugs can delay the progression of RA, but cannot repair the existing bone damage. Stem cell transplantation can make up for this shortcoming: repair the bone damage in RA and reduce the disability rate. At present, there are more and more emerging research projects. It is foreseeable that with the continuous development of science and technology, the unremitting efforts of R&D personnel and the continuous disclosure of the etiology of RA, its treatment will be safer and more effective.

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