Research Progress of Monoclonal Antibody Drugs Related to Rheumatoid Arthritis

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovitis, joint destruction, and systemic complications. The pathogenesis of RA is caused by immune dysfunction, and key inflammatory mediators such as tumor necrosis factor - α (TNF - α), interleukin-6 (IL-6), and IL-1 play a central role in disease progression. The progress of targeted biotherapy has completely changed the treatment of RA, especially monoclonal antibodies (mAbs) that selectively inhibit these pro-inflammatory cytokines. This review explores the pathogenesis of RA, with a focus on the roles of TNF-α, IL-6, and IL-1 in synovitis and joint degeneration. It also discusses the progress of mAb based therapies, including TNF-α inhibitors (such as adalimumab), IL-6 receptor antagonists (such as tocilizumab), and IL-1 blockers (such as anakinumab). Clinical trials have shown that these biologics can significantly improve disease activity, joint protection, and overall patient prognosis, especially in patients who have poor response to traditional synthetic anti rheumatic drugs (csDMARD). In conclusion, mAb based therapy significantly improves the prospects of RA treatment, providing targeted and effective options for disease control, further optimizing RA treatment, minimizing disease progression, and improving patients' quality of life.

Keywords: Rheumatoid arthritis, cytokines, monoclonal antibody drugs.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation, joint destruction, and various extra-articulate manifestations. Affecting approximately 0.5-1% of the global population [1], compared with men, women have a higher incidence of illness. Owing to the progressive joint damage and functional impairment caused by RA, if left untreated, it can significantly reduce the quality of life [2]. The exact cause of RA is still unclear, and the core of its pathogenesis is abnormal immune response, which can cause chronic inflammation, mainly mediated by pro-inflammatory cytokines, activated immune cells, and autoantibodies. Over the past few decades, advances in the understanding of RA disease and mechanisms, that shifted therapeutic approaches form nonspecific immunosuppression to targeted biological therapies. Among these, monoclonal antibody (mAb) drugs have emerged as a transformative class of therapeutics, revolutionizing the management of RA by specifically targeting key molecules and pathways involved in the disease process [3].

mAb are laboratory-engineered immunoglobulins designed to bind with high specificity to particular antigens, such as cytokines, cell surface receptors, or immune cells. The development of tumor necrosis factor - α (TNF - α) inhibitors marks the first major breakthrough in this field, greatly improving disease control for many RA patients. After the success of TNF - α inhibitors, other mAb targeting co stimulatory pathways such as interleukin-6 (IL-6), CD20, and CTLA-4 have also been developed, further expanding the treatment options for RA. Although these therapies are effective, they are not universally effective and still face challenges such as drug resistance, adverse reactions, and variable patient responses [3].

This article will provide an overview of the pathogenesis of RA and describe the research progress of mAb drugs in the treatment of RA. This article will explore its mechanism of action, clinical efficacy, and comparison with other drugs. In addition, this article will also discuss the challenges and prospects of mAb drug therapy.

2. The Pathogenic Mechanism of RA and Key Pathogenic Factors

The pathogenesis of RA involves complex interaction between genetic predisposition, environmental triggers, and immune dysregulation, resulting in persistent inflammation and bone erosion. Among them, the key pathogenic factors in RA are derived by the activation of immune cells and pro-inflammatory cytokines, mainly TNF-α, interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines maintain chronic inflammation in the joints by promoting immune cell infiltration, synovial hyperplasia, and osteoclast activation, ultimately leading to joint deformity and systemic complications [4].

2.1. TNF-α in RA

TNF-α is a member of the TNF superfamily, which is produced mainly by monocytes, fibroblast-like synoviocytes (FLS), activated T cells and dendritic cells in response to infection, immune activation, and cellular stress. It exists in two forms: membrane-bound TNF-α and soluble TNF-α, both of which exert biological effects through two different receptors TNF receptor 1 (TNFR1) and TNFR2. TNFR 1 expressed ubiquitously on most cell types, and it contains a death domain, triggering pro-inflammatory signaling, apoptosis, cytokine production and synovial fibroblast activation. TNFR2 mainly exists in endothelial cells, and myeloid cells, lakes a death domain and playing a regulatory role in immune homeostasis. The imbalance between the production and regulation of TNF-α is one of the causes of chronic inflammation and tissue damage observed in RA. In RA, excessive production of TNF-α in the synovial leads to persistent inflammation and autoimmunity. It plays a crucial role in activating FLS, which are the main cells responsible for synovial hyperplasia and the formation of pannus formation. TNF-α stimulate FLS proliferation and produce matrix metalloproteinases (MMPs) that can degrade extracellular matrix and collage and cause cartilage destruction. Agglomerase proteoglycans have also been produced for the decomposition of cartilage proteoglycans. In addition, TNF-α upregulates osteoclast activation factors, inhibits osteoprotegerin (OPG), and induces osteoclast precursor migration, thereby stimulating osteoclast differentiation and bone resorption. The net effect of TNF-α-driven signaling is progressive joint damage, leading to pain, stiffness, and functional loss in RA patients. In addition to local joint damage, TNF-α can also cause systemic inflammation and autoimmunity. It activates B cells to produce rheumatoid factor (RF) and anti citrullinated protein antibodies (ACPA), which form immune complexes that drive inflammation and synovial infiltration of macrophages and neutrophils. These immune complexes activate the complement pathway, further exacerbating inflammation. TNF - α also recruits and activates T cells, especially Th1 and Th17 cells, which produce additional pro-inflammatory cytokines such as IL-6 and IL-17, thereby continuing the inflammatory cycle. In the vascular system, TNF-α upregulates vascular endothelial growth factor (VEGF), promoting angiogenesis and increasing vascular permeability, thereby allowing more immune cells to infiltrate the synovium. The sustained activation of the TNF-α pathway can lead to systemic complications, including cardiovascular disease, osteoporosis, and fatigue in RA patients [5].

2.2. Pathogenic Role of IL-6 in RA

IL-6 is produced by macrophages, FLS, T cells and endothelial cells in response to inflammation, infections, or tissue damage. Its effects through two main signaling pathways: classical signaling and Trans-signaling, compared with classical signaling the Trans-signaling is more related to chronic inflammation and is highly relevant in RA, even inflammatory cells lack mIL-6R but respond to IL-6 through soluble IL-6receptor, this activates gp130 on immune cells, fibroblasts, and osteoclasts, promoting chronic inflammation, immune dysregulation and bone resorption. In the synovial microenvironment, IL-6 is the main driving factor for the activation of synovial fibroblasts. It promotes the proliferation and migration of FLS, leading to immune cell infiltration into the synovium. IL-6 also induces the production of VEGF, promotes angiogenesis and increased vascular permeability, and facilitates the migration of immune cells to joints. In addition, IL-6 enhances the

production of MMPs, especially MMP-1, MMP-3, and MMP-13, which degrade collagen and proteoglycans. IL-6 reduces the synthesis of cartilage protective molecules and accelerates cartilage breakdown. These form a self-sustaining inflammatory cycle, leading to chronic joint inflammation and injury. In addition to synovitis, IL-6 also plays a key role in osteoclast genesis and bone erosion in RA. It induces the expression of nuclear factor kappa B receptor activator (RANKL) on osteoblasts and fibroblasts, thereby stimulating osteoclast differentiation and bone resorption. IL-6 also inhibits osteoblast function, preventing bone formation and repair. The imbalance between bone resorption and bone formation leads to progressive bone erosion, joint deformities, and systemic osteoporosis in RA patients. Excessive osteoclast activity is a hallmark of erosive RA, and patients may experience severe joint damage over time. IL-6 is also a key regulator of immune system activation and autoimmunity in RA. It promotes the differentiation of B cells into plasma cells that produce antibodies, thereby increasing the production of RF and ACPA. These autoantibodies contribute to the formation of immune complexes, further activating the complement pathway and maintaining inflammation. IL-6 promotes Th17 expression while inhibiting regulatory T cells, leading to loss of immune tolerance. Th17 cells secrete IL-17, which is another pro-inflammatory cytokine that can promote synovitis and bone destruction. In addition to joint pathology, IL-6 also plays an important role in the systemic manifestations of RA. It stimulates the production of C-reactive protein (CRP) in the liver, making it a biomarker of disease activity. IL-6 also promotes the production of hepcidin, leading to chronic anemia by reducing iron utilization. Elevated IL-6 levels are associated with fatigue, depression, and cognitive impairment, which are common in RA patients. In addition, IL-6 will lead to cardiovascular complications, including endothelial dysfunction, atherosclerosis and increased risk of myocardial infarction, making RA patients more prone to heart disease [5, 6].

2.3. Pathogenic Role of IL-1 in RA

IL-1, as an effective pro-inflammatory cytokine, has two biologically active forms, namely IL-1 α and IL-1 β, both of which bind to IL-1 receptors (IL-1Rs) and mediate inflammatory signaling. In addition, IL-1 activity is regulated by IL-1R antagonists, which competitively bind to IL-1R for continuous IL-1 signaling without inducing a response.

In RA, IL-1 is mainly produced by macrophages, fibroblast like synovial cells (FLS), neutrophils, and dendritic cells, and its excessive production can lead to chronic inflammation and joint damage. IL-1 recruits MyD88 through IL-1R1, thereby activating the NF-κB and MAPK pathways, promoting the transcription of pro-inflammatory cytokines (TNF-α, IL-6), matrix metalloproteinases (MMP), and chemokines, leading to the recruitment of immune cells into inflamed synovium. IL-1 also promotes its proliferation by activating FLS, leading to the formation of vascular opacities. It can also stimulate the production of VEGF to induce angiogenesis and promote immune cell infiltration. In addition, IL-1 induces cartilage damage by stimulating MMP (MMP-1, MMP-3, MMP-13), which degrades extracellular matrix components and inhibits the synthesis of cartilage protective proteins (aggrecan, type II collagen). In terms of bone metabolism, IL-1 enhances osteoclastogenesis by increasing RANKL expression and inhibiting osteoprotegerin (OPG), leading to bone resorption and joint deformities.

In addition, IL-1 plays an important role in autoimmune disorders as it promotes B cell differentiation and the production of RF and ACPA, which form immune complexes and sustain inflammation. IL-1 can also induce T cell differentiation towards the Th17 pathway, increase IL-17 production, and further exacerbate synovitis and osteoclast activity. In addition to joint pathology, IL-1 also has systemic effects on RA, including fever, fatigue, chronic disease anemia (up-regulated by calmodulin) and cardiovascular complications, because it plays a role in the progression of atherosclerosis [7].

3. Research Progress of mAbs

mAbs are laboratory generated antibodies designed to target specific antigens and play a crucial role in modern immunotherapy. The basic principle of mAb production is based on the fusion of immortal myeloma cells with antigen-specific B lymphocytes, resulting in hybridoma cells that can continuously proliferate and produce a single type of antibody. This technology was first developed by Köhler and Milstein in 1975 and is capable of generating highly specific antibodies for therapeutic, diagnostic, and research applications [8].

3.1. Principle of mAbs in RA

The characteristic of RA is the excessive production of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-1, these cytokines can cause inflammation, synovial hyperplasia, and joint destruction. MAbs exert their effects by binding to these cytokines or their receptors, preventing them from activating signaling pathways [9].

3.2. MAb drugs targeting TNF-α—Adalimumab

Adalimumab is a fully human mAb specifically targeting TNF-α, a key cytokine involved in the pathogenesis of RA. Adalimumab was approved by the FDA in 2002 and significantly changed RA management by reducing inflammation, joint damage, and disease progression. As a biological anti rheumatic drug (bDMARD), it is used for moderate to severe RA patients with poor response to traditional synthetic DMARD (csDMARD) such as methotrexate (MTX) [10]. Adalimumab acts by binding to soluble and membrane-bound TNF - α, preventing its interaction with TNF receptors on immune cells, thereby inhibiting inflammatory signaling cascades such as NF-κ B and MAPK pathways. TNF - α is the main driving factor for synovial inflammation, formation of vascular opacities, cartilage degeneration, and activation of osteoclasts, all of which can lead to joint pain, swelling, and long-term disability in RA patients [11]. By neutralizing TNF - α, adalimumab helps to inhibit synovial inflammation, reduce leukocyte infiltration, and decrease bone resorption, thereby improving physical function and quality of life.

The clinical efficacy of adalimumab in the treatment of RA has been fully demonstrated through numerous randomized controlled trials (RCTs) and real-world studies. The DE019 and PREMIER studies have shown that adalimumab, especially when used in combination with MTX, can significantly reduce disease activity score (DAS28), joint injury, and radiological progression. Patients receiving adalimumab combined with MTX treatment have a higher response rate compared to those receiving monotherapy, highlighting the benefits of combination therapy. In addition, long-term data from open label extension studies confirm that adalimumab maintains sustained efficacy and disease control over several years of treatment. It is particularly beneficial for early RA patients, as early intervention with TNF inhibitors such as adalimumab has been shown to prevent irreversible joint deformities. The ACR20, ACR50, and ACR70 response rates (measured as 20%, 50%, and 70% improvement in RA symptoms, respectively) were consistently high in patients treated with adalimumab, which reinforces its role as an effective biologic therapy for RA [11-13].

3.3. MAb drugs targeting IL-6—Tocilizumab (TCZ)

TCZ is a humanized mAb that selectively inhibits interleukin-6 receptor (IL-6R) and plays a crucial role in the treatment of moderate to severe RA. IL-6 is a pro-inflammatory cytokine that contributes to the pathogenesis of RA by promoting synovitis, autoantibody production, osteoclast activation, as well as systemic manifestations such as anemia, fatigue, and cardiovascular risk. TCZ was approved by the FDA in 2010 and is particularly effective for patients with insufficient response to traditional DMARDs (such as methotrexate) or TNF inhibitors (such as adalimumab and infliximab). The mechanism of action of TCZ includes binding to soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), preventing IL-6 from interacting with its receptors and activating downstream inflammatory pathways such as JAK/STAT, MAPK, and PI3K/Akt signaling. IL-6

works through two signaling mechanisms: classical signaling and trans signaling, by blocking two signaling pathways, TCZ can significantly reduce synovial hyperplasia, immune cell recruitment, angiogenesis, and osteoclastogenesis, thereby alleviating inflammation, protecting joints, and controlling overall disease in RA patients.

Clinical trials such as OPTION, RADATE, TOWARD, AMBITION, and LITHE have demonstrated the effectiveness of TCZ in treating RA, particularly in patients with methotrexate resistance and TNF inhibitor resistance. In the OPTION trial, patients receiving TCZ+MTX treatment had significantly higher ACR20, ACR50, and ACR70 response rates than patients receiving only MTX treatment. Similarly, the RADATE trial confirmed that TCZ is effective in patients who have previously failed TNF inhibitor treatment, with a higher DAS28 response rate compared to placebo. The evidence provided by the AMBITION trial indicates that TCZ monotherapy is superior to MTX monotherapy, making it a suitable alternative for patients who cannot tolerate MTX. In addition, LITHE experiments have shown that TCZ can slow down the radiological progression of joint injuries and enhance its potential to improve the disease. These research results confirm that TCZ, whether used as a monotherapy or in combination with MTX, is an efficient treatment option for RA. Due to its strong therapeutic effect, TCZ has been included in the EULAR and ACR guidelines for the treatment of moderate to severe RA, especially for patients who do not respond to TNF inhibitors [14].

3.4. MAb drugs targeting IL-1—Anakinra

Anakinra works by competitively binding to the IL-1R1, preventing IL-1 α and IL-1 β from exerting their inflammatory effects. This can reduce synovial hyperplasia, decrease the release of inflammatory cytokines, inhibit osteoclastogenesis, and prevent cartilage damage. In 2001, Anakinra was approved by the FDA as the first biological IL-1 inhibitor for the treatment of RA, although its use has since been largely replaced by TNF inhibitors and IL-6 inhibitors as they have better efficacy for most RA patients. However, Anakinra remains an important treatment option for specific patient populations, especially those with systemic autoimmune diseases and RA patients who are resistant to other biologics, as well as moderate to severe patients who do not respond to initial anti rheumatic drugs.

Clinical trials have shown that daily use of 50-100 mg of Anakinra can significantly increase the proportion of RA patients achieving ACR20. If 50-150 mg of Anakinra is used daily, patients also show significant improvement in ACR50, ACR70, HAQ, and ESR scores, increase in ACR50/70 rate, decrease in HAQ score, and decrease in ESR indicate that the patient's RA symptoms are improving, inflammation is decreasing, and overall joint function is better. However, the efficacy of Anakinra is lower than that of TNF inhibitors or IL-6 inhibitors, which limits the application of anakinra as a first-line biological therapy for RA, especially since newer biologics have shown stronger inhibitory effects on the inflammatory pathway. However, Anakinra are still used in specific cases, especially in patients with comorbidities such as recurrent infections, macrophage activation syndrome (MAS), or autoinflammatory syndromes (such as Still's disease, systemic juvenile idiopathic arthritis). In addition, Anakinra have been proven effective in patients who cannot tolerate TNF inhibitors or MTX [15].

4. Conclusion

RA remains a major challenge in the field of rheumatology due to its chronic nature, complex pathogenesis, and serious impact on patients' quality of life. The advances in immunology and molecular biology have paved the way for targeted biological therapies, especially mAbs, which have completely revolutionized RA treatment. This article explores the pathogenesis of RA, emphasizes the key role of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, and reviews the development and efficacy of mAbs targeting these molecules. The pathophysiology of rheumatoid arthritis is caused by abnormal immune responses, which can lead to persistent synovial inflammation,

joint destruction, and systemic complications. TNF - α plays a central role in maintaining inflammation, promoting synovial hyperplasia, and inducing osteoclast mediated bone resorption. Similarly, IL-6 can lead to systemic manifestations such as synovitis, autoantibody production, anemia, and cardiovascular risk. IL-1 further exacerbates inflammation by stimulating immune cell recruitment, synovial proliferation, and matrix degradation. Given the crucial role of these cytokines in the pathogenesis of rheumatoid arthritis, they have become the main target of therapeutic interventions. mAb-based therapy significantly improves disease management by specifically targeting cytokines and immune pathways associated with RA. For example, adalimumab, tocilizumab, and anakinumab can effectively alleviate and treat symptoms, especially for patients who have not responded well to traditional therapies. However, mAb therapy still faces challenges. The varying responses of patients to mAb therapy highlight the necessity of precision medicine methods, including pharmacogenomics, to identify predictive factors for treatment response and optimize treatment options. In addition, long-term safety issues such as increased risk of infection, malignant tumor potential, and immunogenicity must be carefully monitored. The high cost of mAbs also poses a significant barrier to accessibility, especially in resource limited environments, highlighting the need to develop biosimilars to improve affordability. In the future, research on RA treatment should focus on improving existing biologics, developing new targets, and exploring combination therapies to enhance treatment efficacy. The advancement of biotechnology such as bispecific antibodies and small molecule inhibitors provides promising avenues for addressing treatment resistance and improving disease outcomes. In addition, early intervention strategies and personalized treatment plans based on patient specific biomarkers can further optimize RA management, minimize disease progression, and improve long-term prognosis.

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