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Trends of Treatment Development in Rheumatoid Arthritis: Promise, Progress, and Challenges

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Abstract

Rheumatoid arthritis (RA) is a chronic, systemic, abnormal inflammatory immune response. It is characterized by the involvement of the synovium and multiple organs and the destruction of joints and articular cartilage. In the past 30 years, several promising novel compounds and antibodies have been developed for the treatment of RA. The introduction of new drugs and precision medicine for all forms of RA raises several issues related to access to novel treatments by patients, optical regimen selection, cost-effectiveness, prognosis monitoring and outcome surveillance, particularly with regard to the development of low drug response rates, drug resistance and adverse side effects. Tremendous attention has been given to the identification of optimized drug combinations for the treatment of RA, particularly in early high-risk vulnerable and early individuals. Addressing these issues requires novel therapeutic approaches with new mechanisms and the establishment of accurate guidelines for drug selection, drug recombination, and non-chemical therapeutic efforts. In this study, we reviewed the most exciting recently established or ongoing novel drugs and approaches according to the clinical trial database maintained by the United States National Library of Medicine and discussed the trends in RA drug development and challenges in the treatment, providing a reference significant for the accurate treatment of RA and the research direction in the future.

Key words: rheumatoid arthritis; precision medicine; new treatment; drug development; method development

1. Introduction

The treat-to-target (T2T) strategy is the general principle of RA treatment [1]. The treatment goal for patients with RA is to control inflammation while retaining joint structure and function [2], prevent structural damage, and restore

normal human function to maximize the quality of life [3]. Therefore, appropriate diagnosis and treatment are needed in the early stages of the disease. Currently, glucocorticoids, anti-inflammatory drugs, and disease-modifying antirheumatic drugs (DMARDs) are used for clinical treatment. DMARDs include conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biological DMARDs (bDMARDs). These drugs have been proven to be effective in improving the condition of patients with RA [4]. By maintaining remission, these drugs have also been shown to prevent joint destruction and progression of physical dysfunction over a long period. With the advances in diagnosis and treatment technology, molecular targeted therapy based on small molecules makes treatment based on the pathological mechanism of RA possible. At the same time, molecular targeted therapy strategy is also applied to a variety of autoimmune diseases [5]. New innovations are constantly being made to the existing therapeutic drugs and treatment methods of RA, and new treatment has been introduced in many new studies, and clinical drug trials are in progress. This article summarizes the latest therapeutic drugs and methods for the treatment of RA, in order to provide more and newer treatment schemes for the clinical treatment of RA. In this article, ClinicalTrials.gov (https://clinicaltrials.gov/) were searched for clinical trials between 2017 and 2022, using "Rheumatoid Arthritis", "Recruiting and not yet recruiting studies" and "Clinical Trial"as keywords. Finally, a total of 207 clinical trial studies on RA was found (See Figure 1). On the one hand, the results show that there is a significant regional imbalance on the treatment of RA in the world, which is mainly concentrated in economically developed regions such as China, the United States and the European Union. Therefore, the treatment of RA patients in underdeveloped countries will be difficult and may still be a backward level. Moreover, the new drug therapies include immune cell regulatory drugs, cytokine inhibitors, and stem cell therapy (See Table 1). In addition, a number of new therapeutic methods are also being tested in clinical trials, including PET radioligands, ultrasound therapy, nerve stimulation, diet and joint function exercise (See Table 2). This review summarizes new drugs and methods used for the treatment of RA in the recent 6 years to provide more treatment strategies for RA.

2. Disease-modifying antirheumatic therapy

In recent years, T2T treatment strategies and a variety of targeted drugs have been gradually introduced into the treatment of RA. Accurate treatment slows down the development of the disease and plays a positive role in the control of RA. In recent years, with the in-depth study of RA, it is gradually found that some immune cells and cytokines are involved in the pathogenesis of RA. Biological therapy for different links in the pathogenesis of RA has become one of the current research hotspots, especially with the emergence of monoclonal antibody drugs, such as monoclonal antibody drugs targeting T cells, B cells, and cytokines (See Figure2). The long-term efficacy and safety of these drugs are supported by abundant clinical data. In addition, many targeted drugs have been approved for use or are in the trial stage.

2.1 Monoclonal antibody therapy targeting T cells

The activation of antigen-specific T cells has always been considered to be the central link in the pathogenesis and progression of RA. T cells accumulate and activate in the inflammatory synovium. Through the secretion of interferon γ (IFN-γ) and interleukin 17 (IL-17) and direct cell-cell interaction, different subsets of T cells play different roles in the pathogenesis of RA [6]. About T cell subsets with specific functions, such as helper T cell 17 (Th17), cytotoxic T cell (CTL), and regulatory T cell (Treg), play an important role in the pathogenesis of RA. Activated T cells can also promote RA bone injury by secreting osteoprotegerin ligand (OPGL) and participate in the pathological process of RA by producing inflammatory mediators. It is suggested that the therapy of regulating intra-articular T cells may achieve the ultimate goal of lasting cure of diseases [7,8]. Therefore, a correct understanding of different subsets of T cells in the pathogenesis of RA is important to explore new strategies for the treatment of RA and to develop new drugs. Abatacept is a selective T cell costimulatory regulatory protein produced by recombinant deoxyribonucleic acid (DNA) [9]. It inhibits the activation of T cells related to the pathogenesis of RA by binding to CD80 and CD86 on antigen presenting cells (APCs). Abatacept exists largely in the synovium of patients with RA. By binding to CD80 and CD86 on APCs, it blocks the interaction with CD28 on T cells, thus inhibiting the activation of T cells and playing a role in the treatment

of RA [10]. In 2020, Abatacept, which was officially listed in China, is the first T cell selective costimulatory immunomodulator in the world. Previous studies have shown that Abatacept has a clinical effect similar to that of TNF inhibitors, and has a more obvious effect on delaying bone destruction [11]. Compared with methotrexate (MTX) alone, Abatacept combined with MTX can reduce the level of anti-CCP antibody in more patients [12,13]. At present, five clinical studies are evaluating the efficacy and safety of Abatacept (NCT04120831, NCT03619876, NCT03669367, NCT03733067 and NCT03652961). In the next 10 years, Abatacept will be widely used in the treatment of RA, especially in anti-CCP positive patients. It is one of the hot drugs for RA in the future. In addition, there are also various T-cell-targeting drugs in clinical trials, including VIB4920 (NCT04163991), KN019 (NCT04038970) and KPL-404C (NCT05198310)。Targeting the CD40-CD40L pathway may be an effective way to treat autoimmune diseases, including RA [14]. VIB4920 is a novel engineered antagonist that can inhibit T cells activation and blocks CD40L. KN019, a recombinant human CTLA-4 variant Fc fusion protein injection that can compete with CD28. KPL-404C is an anti-CD40 antibody and can inhibit T cell-mediated activation of B cells. Currently, they are in the initial stage of clinical trials, and the research data are not supported enough. With the continuous progress of research, these drugs have the opportunity to be candidates for the treatment of RA. It has been reported that other types of T cell studies have also shown initial results. Abnormal regulation of follicular helper T (Tfh) cells and memory T (Tm) cells is also found in patients with RA, which plays an important role in the occurrence, development and pathological process of the disease. In the future, the in-depth study of Tfh cells and Tm cells will help to further clarify the pathogenesis of RA and explore new therapeutic targets [15,16]. Different subsets of T cells play different roles. Although the current research on T cells is not in-depth, it is difficult to develop related drugs. However, with the discovery of the broader role of T cells in the pathogenesis and progression of RA, the treatment of RA by regulating T cells will develop rapidly and have great therapeutic potential. A correct understanding of the role of different subsets of T cells in the pathogenesis of RA is of great significance for exploring new strategies for RA and developing new drugs.

2.2 Monoclonal antibody therapy targeting B cells

More and more studies have found that B cells are also involved in the pathogenesis of RA through a variety of ways. B cells become APCs by self-reaction, which leads to the activation of T cells [17]. Activated T cells activate macrophages to produce pro-inflammatory cytokines, leading to joint inflammation and destruction. In addition, B cells themselves can also produce TNF-α, IL-6 and lymphotoxin, leading to the further development of inflammation [18,19]. At present, therapy targeting B cells is mainly aimed at CD molecules, especially CD20 antigen. It has been found that CD20 is expressed on the surface of B cells and participates in regulating the growth and differentiation of B cells. It is an ideal site for immune clearance of B cells [20]. Rituximab is a kind of monoclonal antibody specific to the CD20 molecule, which can be bind to the CD20 on the surface of B lymphocytes and specifically clear B lymphocytes through complement-mediated cytotoxicity and other mechanisms, so as to achieve the therapeutic effect [21]. Previous studies have shown that B cells play a key role in the pathogenesis of RA through multiple mechanisms [22]. And rituximab is effective and safe for RA. Similar to the mechanism of rituximab, mabionCD20 is a new CD20 antibody. A clinical trial is under way in 280 patients. It is expected to become a new type of biomimetic drug of rituximab in the future and has strong therapeutic potential. In the study of anti-CD22, SM03 is the first anti-CD22 chimeric monoclonal antibody used to treat RA during the clinical research phase. The results of some clinical studies showed that SM03 combined with MTX have significant clinical efficacy and good drug safety tolerance during the 24-week course of treatment (NCT04312815). In patients with active RA treated with MTX, SM03 was effective, safe, and well-tolerated throughout the 24-week treatment [23]. The follow-up clinical study of SM03 is still in progress, and the sample size will be expanded to obtain more data support. Another drug that acts on B cells is ianalumab, which is a human monoclonal antibody (mAb) of type IgG1/κ binding to B-cell activating-receptor, and can deplete B cells and blocks activating. The study, which will include 50 RA patients, began clinical trials in 2018 and is still under way (NCT03574545). It is not difficult to find that biotherapy targeting B cells has become a new hot spot, which has great potential in RA. However, compared with T cells, there are relatively few studies on B cells in the field of RA, and they are mainly focused on CD20 antigens. To study more CD molecules and form a connection with T cells will be one of the main research directions in the field of B cells in the future.

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2.3 Monoclonal antibody therapy targeting cytokines

Janus kinase (JAK) is a family of non-receptor tyrosine kinases that bind to specific cytokine receptors. The substrate of JAK is a signal transducer and activator of transcription (STAT), which can form the JAK-STAT signal pathway and play an important role in the pathological process of RA [24]. It has been reported that a large number of inflammatory factors such as TNF and IL-6 have been found in the articular cavity of patients with RA. These factors are important participants in the pathogenesis of RA and joint destruction, and can activate JAK/STAT signal pathway through different pathways. JAK inhibitors are new types of small-molecule targeted synthetic drugs, which can selectively inhibit JAK kinase and block JAK/STAT signal pathway, can play a role in all stages of RA [25]. Tofacitinib is the first oral JAK1/3 inhibitor approved in China for the treatment of RA [26]. Studies have shown that Tofacitinib can inhibit the production of inflammatory cytokines such as TNF, IL-6 and IL-1β, and significantly reduce inflammatory cell infiltration and bone resorption. At the same time, it can also inhibit the activation of many kinds of cells and cytokines, relieve inflammation and reduce joint injury [27]. In addition, clinical data on JAK inhibitors with different selectivity have been reported. Similar to the JAK1/2 inhibitor baricitinib [28] and JAK1 inhibitor upadacitinib [29] and filgotinib [30], all of which have recently been approved for the treatment of moderate to severe RA. The novel JAK1 inhibitor SHR0302, JAK3 inhibitor peficitinib [31], and decernotinib [32], and JAK3/TEC inhibitor ritlecitinib [33] , and JAK1/TYK2 inhibitor TLL-018 (NCT05133297) currently being studied for RA. At present, the clinical research on JAK inhibitors is very hot, and a number of projects are under way to study the efficacy and safety of different types of JAK inhibitors in the treatment of RA (NCT05246293, NCT05238896, NCT05153200, NCT04985435). After recognizing that disordered JAK-STAT signaling is not the only pathogenesis of RA, exploring the combination therapy of JAK inhibitors may maximize the therapeutic efficiency and make up for the lack of RA response in the treatment of DMARDs alone, such as combination of baricitinib and adalimumab (NCT04870203). To sum up, as a new type of oral small molecule targeted drugs, JAK inhibitors have completely changed the treatment of immune and inflammatory diseases. The successful application in the field of RA has broken the treatment of traditional rheumatic drugs and biological drugs. Compared with traditional therapeutic drugs and biological antirheumatic drugs, it has the advantages of improving condition, good safety and convenient oral use, which provides a new therapeutic strategy for RA and has the same therapeutic status as biological agents [1,34]. At present, research and development of JAK inhibitors are very popular. Based on the functional characteristics and special tissue distribution of various subtypes of JAK kinase family, JAK1 and JAK3 have become hot targets in the field of autoimmune and inflammatory diseases. In recent years, with the in-depth study of its mechanism, JAK inhibitors are also expanding in clinical application, and are the star products in the treatment of RA [25].

In the pathogenesis of RA, inflammatory cells stimulate the release of pro-inflammatory mediators such as IL-6, which leads to the destruction of intra-articular structure. IL-6 is mainly produced by endothelial cells and T cells, and stimulates B cells to produce antibodies and immunoglobulins to activate effector T cells. IL-6 can also induce vascular epithelial cells to form pannus, activate adhesion molecules on vascular endothelial cells, and induce immune inflammatory response [35]. Olokizumab (OKZ) is an IL-6 monoclonal antibody that can directly bind to IL-6 at specific sites. The results showed that there were significant differences in all secondary efficacy endpoints between the OKZ group and the placebo group, and more patients in the OKZ group reported adverse events (AEs), of which infection was the most common [36]. In conclusion, OKZ has more significance in the treatment of RA and has a high therapeutic potential value. Its long-term safety and efficacy have also been studied (NCT04246762). In addition, BCD-089 (NCT04227366), a therapeutic monoclonal antibody that binds to the IL-6 receptor (IL-6R), and gerilimzumab (NCT04179513), a drug targeting IL-6 cytokines, are currently undergoing clinical trials on their safety and tolerance. The world's first anti-IL-6 anti-inflammatory drug, sarilumab, was approved in 2017. Sarilumab is the first humanized monoclonal antibody that directly targets IL-6Rα, which can specifically bind to the IL-6 receptor [37]. In a phase III study, sarilumab is significantly superior to adalimumab in improving signs, symptoms, and body function, and the safety of the two drugs is as expected [38]. At present, sarilumab is already under way phase IV study (NCT04350216). Although the aetiology of RA remains to be fully elucidated, IL-17 are believed to play a critical role in the pathogenesis of RA. IL-17 is not only a powerful inflammatory cytokine, but also a fine-tuning factor of inflammatory response. It

can stimulate fibroblasts, epithelium and endothelial cells to release cytokines such as IL-6, IL-8 and GM-CSF, and cooperate with a variety of cytokines to amplify the inflammatory response [39]. IL-17 can also induce human fibroblasts to express intercellular adhesion molecules and promote T cell proliferation. Recently, monoclonal antibodies against IL-17 have been shown to be safe and effective in early clinical trials of RA [40]. Secukinumab was the first IL-17A inhibitor used to treat psoriasis [41]. In a RCT study for RA, secukinumab (150mg) showed efficacy in patients with RA with insufficient response to TNF-α inhibitors, but a large sample of long-term trial results is needed for verification [42]. In addition, a clinical study of rebamipide on RA has been launched (NCT05166304). Rebamipide is an antiulcer drug that protects gastric epithelial cells, and improves gastric defense mechanisms by increasing gastric mucus. Rebamipide inhibited IL-17, also it inhibits IL-1β-induced RASF proliferation. As the research progresses, rebamipide may have new indications. Compared with IL-17 and IL-1, the study on IL-6 is more mature in the treatment of RA. At present, there are two main types of IL-6 inhibitors in clinical research: targeted IL-6 and targeted IL-6R [43,44]. In theory, the level of IL-6 is various in different patients, while IL-6R has little difference between individuals. Therefore, it may be easier to develop therapeutic drugs targeting receptors. However, blocking ligands is more direct than blocking IL-6 receptors, so which strategy has more advantages is a difficult choice. IL-6 is a key mediator in the inflammatory process of RA and has high levels in serum, synovial tissue and synovial fluid of patients with RA [45,46]. Therefore, it is a very attractive target for the study of new therapies for RA in the future.

Granulocyte-macrophage colony-stimulating factor (GM-CSF), also known as colony-stimulating factor 2 (CSF2), is a monomer glycoprotein. GM-CSF promotes the activation, differentiation, survival and proliferation of monocytes and macrophages transported in inflammatory tissues such as synovial joints of RA. Activated M1 macrophages produce cytokines, including GM-CSF and other pro-inflammatory cytokines. Local GM-CSF production leads to the activation of blood vessels and bone marrow and promotes the differentiation of effector T cells at the inflamed site [47]. Studies have found that the content of GM-CSF is very high in the joints of patients with RA, and using GM-CSF as a biological target can reduce inflammation and damage. Some drugs are being developed to block GM-CSF [48]. The anti-GM-CSF monoclonal antibody, namilumab, can be bind to the GM-CSF ligand with high affinity and effectively neutralize GM-CSF [49]. A phase II efficacy and safety study of namilumab in patients with RA with inadequate response to MTX therapy or ineffective or intolerant biotherapy against TNF showed that it could inhibit the activity of macrophage-targeted GM-CSF and showed a significant dose-dependent response in the treatment of RA [50]. Moreover, Otilimab also is a monoclonal antibody that mainly acts on and inhibits the inflammatory cytokine GM-CSF [51]. In a RCT study, the researchers focused on the clinical effects of Otilimab in preventing inflammation, tissue damage and pain in patients with RA. After administration of different doses of Otilimab and continuous treatment with MTX for 5 weeks, the administration time was prolonged and continued for another 50 weeks. The results showed that Otilimab treatment quickly relieved joint pain and swelling, and the pain score reported by patients is significantly improved. In terms of safety, Otilimab treatment is well tolerated, the incidence of cytopenia and severe infection is very low, there is no significant clinical production of anti-drug antibodies, no clinical death and pulmonary toxicity events, which is consistent with previous studies on other targeted GM-CSF antibodies. Clinical trials of the same drugs, TJ003234, for RA are currently underway. Targeting GM-CSF can not only reduce disease activity, but also significantly improve pain and function, which is a potential research direction for the treatment of RA [52]. Although GM-CSF has been studied for a relatively short time, GM-CSF monoclonal antibodies show obvious advantages in poor response to DMARDs drugs and TNF inhibitors, which provides a new way for the treatment of refractory RA patients [53,54]. In the new era of biological agents, targeting GM-CSF receptors can benefit some active RA, which undoubtedly opens a new therapeutic window. But we should also pay attention to the side effects of GM-CSF monoclonal antibodies, especially in terms of lung function. Because inhibition of GM-CSF signal transduction will interfere with alveolar macrophage clearance of pulmonary surfactant, resulting in alveolar protein deposition.

In the past few decades, the one-drug-one-target theory has achieved great success in guiding the drug research and development of single-cause diseases. However, with the in-depth study of immune diseases, in the face of complex immune regulation network, single target therapy presents some limitations. The strategy of simultaneously targeting two or more targets and regulating multiple targets or pathways to treat diseases has gradually developed, and this treatment strategy usually has better efficacy and fewer side effects. Telitacicept, the first dual-target biological drug independently developed by China, was approved for the treatment of systemic lupus erythematosus in 2021 [55].

Telitacicept is a new type of TACI-Fc fusion protein that has a new drug structure and a double-target mechanism. It can inhibit both BLyS and APRIL cytokines simultaneously, thereby reducing the immune response more effectively and achieving the purpose of treating autoimmune diseases [56]. At present, clinical trials of telitacicept in the treatment of moderate and severe RA have been conducted, and the indications are expected to be further expanded.

The emergence of monoclonal antibody drugs has brought revolutionary changes to the targeted therapy of RA. It plays a role through specific neutralization of cytokines and blocking receptors. It has the advantages of strong targeted, less side effects and good therapeutic effect. However, in the process of application, we should also pay attention to the safety and drug resistance of monoclonal antibody drugs. These deficiencies will also be an important direction for future research. With the continuous development of research, a large number of new monoclonal antibody drugs continue to appear, and the market prospect in the future is still very broad.

2.4 Cell therapy-related novel therapeutic development for RA

Mesenchymal stem cells (MSCs) are pluripotent stem cells that have self-renewal ability and multidirectional differentiation. The ultimate goal of RA treatment is to restore immune tolerance and completely stop immunosuppressive therapy. MSC therapy has attracted wide attention because of its strong immunosuppressive and anti-inflammatory effects [57]. Studies have shown that MSCs can act on Tregs and play an immunomodulatory role, which makes them a potential candidate for the treatment of RA. MSCs were injected intravenously and were followed up for 12 months. The results showed that the levels of Treg-related cytokines, IL-10, and transforming growth factor-β1 (TGF-β1) in the culture supernatant of peripheral blood mononuclear leukocytes increased significantly, reflecting the full immunomodulatory effect of MSCs on Tregs in patients with RA [58]. Hematopoietic stem cells (HSCs) are an adult stem cells in the blood system. It is a heterogeneous population with the ability of long-term self-renewal and the potential to differentiate into all kinds of mature blood cells [59]. Evidence from a study suggests that hemopoietic stem cell transplantation (HSCT) can be effective in the treatment of RA [60]. 33 patients with severe RA were included in the study and were treated with HSCT. The indicators were evaluated 12 months later. It was found that no patient died and no serious AEs occurred. After treatment, 70% of patients achieved ACR20% response. Preliminary results show that HSCT can be safely administered to patients with RA, but larger studies are needed to confirm these findings. At present, there are few clinical studies on HSCs in the treatment of RA, and large-scale trials also have not been carried out, but it has great therapeutic potential and is a research hotspot in the future. Stem cells have strong anti-inflammatory and immunomodulatory functions, as well as repairing joint and osteogenic injuries [61]. It can inhibit the occurrence and progress of inflammation and regulate the autoimmune system by secreting a variety of cytokines, which brings new hope for the treatment of RA [62,63]. At present, a series of clinical trials of stem cells in the treatment of RA has been carried out in the world, include BX-U001 (NCT04971980), hMSC (NCT03186417), HUC-MSC (NCT03828344), Autologous adipose derived stem cells (NCT04170426) and Allogeneic umbilical cord blood (NCT03618784). Through the summary of clinical trials, it is not difficult to find that stem cells become a research hotspot, and a number of clinical trials have been carried out. But we should also recognize that there are still many difficulties in stem cells research. Embryonic stem cells are good, but their sources are limited. At present, embryonic stem cells are mostly obtained from very early embryos of induced abortion or embryos left over from in-vitro fertilization (IVF) [64,65]. In the experiments of hematopoietic stem cells, a set of cell surface markers related to the stage of cell differentiation have been summarized, so that useful stem cells can be isolated from many mixed cell populations. However, whether the stem cell of other cells also have practical cell surface markers or other recognition methods need to be further studied. In addition, the cells and tissues induced by embryonic stem cells are equivalent to allotransplantation for patients, and immune rejection caused by allotransplantation has become an obstacle to stem cells therapy. It is believed that with the continuous development of cell biology and immunology and the continuous improvement of stem cell therapy, the clinical application of stem cell therapy for RA will eventually be realized.

3. Conclusion

Finding targets on the basis of pathophysiology are the main practice concept in the treatment of RA. In the past 20

years, with the rapid development of RA therapy, a large number of new drugs have emerged and been used in the clinic. For example, blocking JAK, IL-6, GM-CSF and inhibiting T cell and B cell consumption have achieved good clinical results. In addition, drug research and clinical trials for new targets are also under way, include ABX464 (NCT04049448), JNJ-67484703 (NCT04985812) and nipocalimab (NCT04991753). Although these latest target drugs provide researchers with new directions and attempts, and are also future research goals, they are still in the stage of small-scale clinical trials and more time is needed to study them. Compared with mainstream drugs such as JAK and IL-6 inhibitors, these latest drugs need to overcome more difficulties and conduct more research in order to successfully become effective drugs in the treatment of RA. In addition to cytokine inhibitors, stem cell therapy with great potential has been developed rapidly, and a large number of studies have proved its safety and effectiveness. These new therapeutic drugs and methods may become an important remedy for the failure of existing DMARDs treatment, and have broad prospects. It is worth noting that although a lot of achievements have been made in the treatment of RA, the current therapeutic drugs are only based on a part of the mechanisms known to be involved in the occurrence and development of RA. The interaction between innate immunity and adaptive immunity and how immune tolerance participate in the pathogenesis of RA is still insufficient. Moreover, in the treatment, there are still some patients with poor response to biotherapy, low effective remission rate and adverse reactions of some drugs. These limitations are one of the difficult problems in the future RA research. In addition to drug therapy, ultrasound therapy (NCT04662359), nerve stimulation (NCT04821050, NCT04539964), diet (NCT04262505) and joint function exercise (NCT05240326, NCT04254146) also play a certain role in the comprehensive treatment of RA patients, which is worthy of further research and exploration. These new methods have their own advantages and disadvantages. Compared with traditional drug therapy, they are unique in relieving symptoms and promoting functional recovery. Some studies on methods of RA are summarized in the world, which are conducive to a better combination of drugs and methods. Clinically, it can be selected according to the specific situation, and combined with drug treatment, so as to learn from each other to achieve the best treatment effect. However, it is worth noting that the new methods can only be used as an adjuvant and not completely replace standardized drug therapy. In summary, currently, the therapeutic drugs and methods for RA are very rich, and new drugs and methods are also being tested in clinical trials. In the context of precision therapy, an efficient, accurate and economical treatment of RA will be our future research direction. The inhibitors of immune cells and inflammatory cytokines, and stem cell therapy will develop rapidly in the next decade, which is also the mainstream direction of the treatment of RA.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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Table 1：RA-related new clinical trial drugs (Recruiting and Not yet recruiting)

Time	State	Clinical trial drug	Target	Clinical trial number
2022	Recruiting	KPL-404	CD40	NCT05198310
2022	Not yet recruiting	Tetrandrine	Chinese Medicine	NCT05245448
2022	Recruiting	Hemay007	TNF-α	NCT05247216
2022	Not yet recruiting	Tofacitinib	JAK1/3	NCT05246293

2022	Not yet recruiting	Baricitinib	JAK1/2	NCT05238896
2021	Recruiting	Advixa	TNF-α	NCT05172817
2021	Recruiting	Tofacitinib	JAK1/3	NCT04928066
2021	Recruiting	Tofacitinib	JAK1/3	NCT04927000
2021	Recruiting	JNJ-67484703	HuIgG1κ	NCT04985812
2021	Recruiting	ABBV-154	TNF	NCT04888585
2021	Recruiting	Nipocalimab	FcRn	NCT04991753
2021	Not yet recruiting	Digoxin/UDCA	Unknow	NCT04834557
2021	Recruiting	Cannabidiol	CB1/CB2	NCT04911127
2021	Recruiting	BX-U001	Tregs	NCT04971980
2021	Not yet recruiting	Spironolactone	Androgen Receptor	NCT05092984
2021	Recruiting	Combination of baricitinib and adalimumab	JAK1/2 and TNF-α	NCT04870203
2021	Not yet recruiting	Rebamipide	IL-17/IL-1β	NCT05166304
2021	Recruiting	TLL-018	JAK1/TYK2	NCT05133297
2021	Not yet recruiting	Adalimumab	TNF-α	NCT05090124
2021	Not yet recruiting	Upadacitinib	JAK1	NCT05153200
2021	Recruiting	Upadacitinib	JAK1	NCT05121298
2021	Recruiting	BC-U001	Unknow	NCT04971980
2021	Recruiting	Paroxetine	GRK2	NCT04757571
2021	Recruiting	Allogeneic adult umbilical cord	Unknow	NCT05003934
2021	Recruiting	Filgotinib	JAK1	NCT04985435
2021	Recruiting	Filgotinib	JAK1	NCT05090410
2021	Recruiting	Vitamin D_2	Unknow	NCT04909931
2021	Not yet recruiting	Luo-Fu-Shan Plaster	Unknow	NCT04884880
2021	Recruiting	Tocilizumab and Sarilumab	IL-6	NCT04842981
2020	Recruiting	Olokizumab	IL-6	NCT04246762
2020	Recruiting	SM03	CD22	NCT04312815
2020	Recruiting	Otilimab	GM-CSF	NCT04333147
2020	Not yet recruiting	L-arginine	Unknow	NCT04535427
2020	Not yet recruiting	MabionCD20	CD20	NCT04680962
2020	Recruiting	SHR0302	JAK1	NCT04333771
2020	Not yet recruiting	BCD-089	IL-6R	NCT04227366
2020	Recruiting	TJ003234	GM-CSF	NCT04457856
2020	Recruiting	Tofacitinib	JAK1/3	NCT04311567
2020	Recruiting	Dietary Fiber Supplementation	Unknown	NCT04421313
2020	Not yet recruiting	Sarilumab	IL-6	NCT04350216
2020	Not yet recruiting	Certolizumab pegol	TNF-α	NCT04569890
2019	Recruiting	ABX464	CBC	NCT03813199
2019	Not yet recruiting	HUC-MSC suspension	Unknown	NCT03828344
2019	Recruiting	Baricitinib	JAK1/2	NCT04086745
2019	Recruiting	ABX464	CBC	NCT04049448
2019	Recruiting	Gerilimzumab	IL-6	NCT04179513
2019	Recruiting	VIB4920	CD40L	NCT04163991
2019	Recruiting	KN019	CD28	NCT04038970
2019	Recruiting	Abatacept	T cell	NCT04120831
2019	Not yet recruiting	Autologous adipose derived	Unknown	NCT04170426

		stem cells		
2019	Recruiting	Metformin	Unknown	NCT04196868
2018	Recruiting	Allogeneic umbilical cord blood	Unknown	NCT03618784
2018	Recruiting	Ianalumab	B cell	NCT03574545
2018	Recruiting	Rupatadine and Montelukast	PAF/H1 and Cysltr1	NCT03770923
2018	Recruiting	Anifrolumab	IFN-1	NCT03435601
2018	Recruiting	Abatacept	T cell	NCT03619876
2018	Not yet recruiting	Abatacept	T cell	NCT03669367
2018	Recruiting	Abatacept	T cell	NCT03733067
2018	Recruiting	Baricitinib	JAK1/2	NCT03755466
2018	Recruiting	Abatacept	T cell	NCT03652961
2017	Recruiting	Telitacicept	BlyS/APRIL	NCT03016013
2017	Recruiting	hMSC	Unknown	NCT03186417

Table 2：RA-related new clinical trial methods (Recruiting and Not yet recruiting)

Time	State	Clinical trial method	Clinical trial number
2022	Not yet recruiting	Pilates training on exercise	NCT05240326
2022	Recruiting	TC99m-tilmanocept imaging	NCT05246280
2021	Not yet recruiting	Plantar massage and textured insoles	NCT05045898
2021	Recruiting	Anti-inflammatory diet	NCT04748809
2021	Recruiting	Cervical stabilization exercises	NCT04948775
2021	Not yet recruiting	Sacral nerve stimulation	NCT04821050
2020	Recruiting	Aerobic exercise	NCT04254146
2020	Recruiting	Ultrasound assessment	NCT04662359
2020	Recruiting	Aerobic exercise	NCT04439682
2020	Recruiting	Hand exercises	NCT04365842
2020	Recruiting	Vagus nerve stimulation	NCT04539964
2020	Recruiting	Mediterranean dietary	NCT04262505
2019	Recruiting	Ultrasound	NCT04084223
2019	Not yet recruiting	OTL38	NCT03938701
2019	Recruiting	PET radioligands	NCT03912428
2018	Recruiting	Ultrasound treatment	NCT03690466
2018	Recruiting	Dietary salt	NCT03649178
2017	Recruiting	Custom Insoles	NCT03170947

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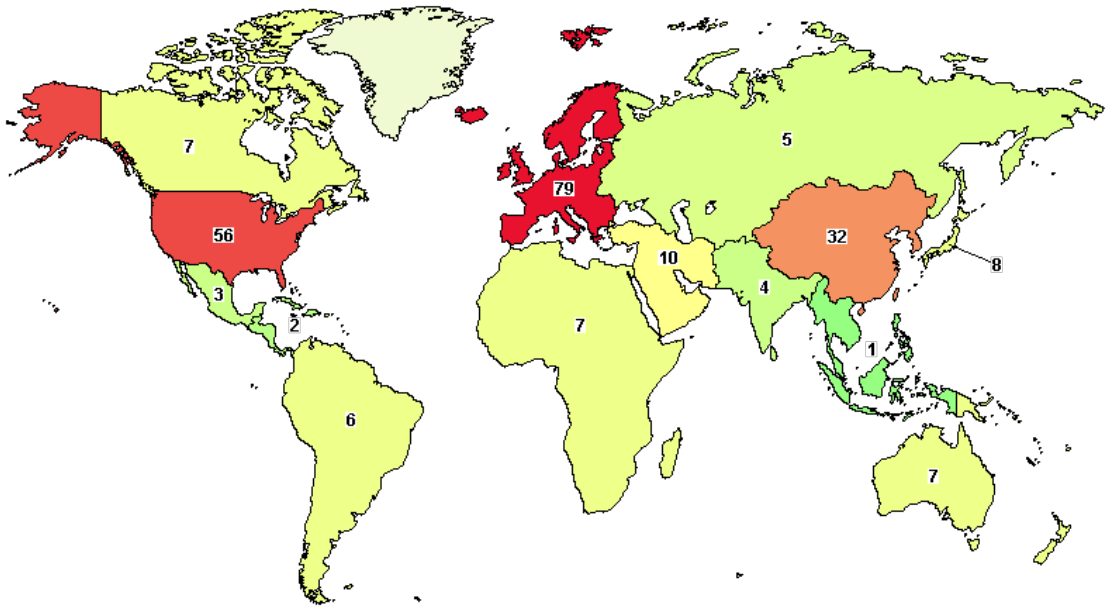

Figure 1 The results of clinical trials between 2017 and 2022. Using "Rheumatoid Arthritis", "Recruiting and not yet recruiting studies" and “Clinical Trial” as keywords to search in ClinicalTrials.gov. Finally, a total of 207 clinical trial studies were found. The number of each area on the picture represents the number of clinical trials currently being conducted in this area, and the number is larger, the more research projects are being conducted. The results show that there is a significant regional imbalance on the treatment of RA in the world, which is mainly concentrated in economically developed regions such as China, the United States and the European Union. Therefore, the treatment of RA patients in underdeveloped countries will be difficult and may still be at a backward level.

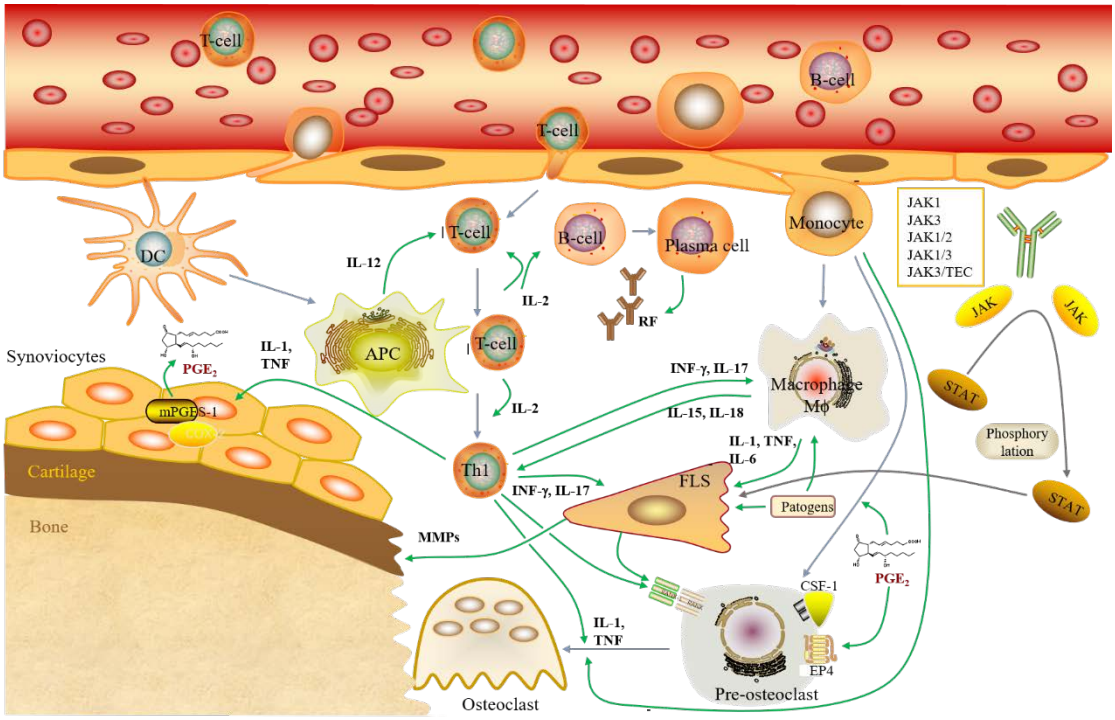

Figure 2 Therapeutic targets and immune cell interactions in Rheumatoid Arthritis. Some immune cells and cytokines are involved in the pathogenesis of RA, such as T cells, B cells, and various cytokines. (1) Th1 cells are CD4+ cells, which differentiate from initial T cells and mainly synthesize IL-2, IFN- γ, IL-1, TNF- α and GM-CSF. Th1 cells promote cell-mediated inflammation by inducing the activation of macrophages, NK cells, B cells and CD8+T cells. (2) B cells become APCs by self-reaction, which leads to the activation of T cells. Activated T cells activate macrophages to produce pro-inflammatory cytokines, leading to joint inflammation and destruction. In addition, B cells themselves can also produce TNF-α, IL-6 and lymphotoxin, and induce plasma cells to produce rheumatoid factor (RF). (3) Janus kinase

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is a non-receptor tyrosine protein kinase. There are four family members, namely JAK1, JAK2, TYK2 and JAK3. JAK inhibitors can selectively inhibit JAK kinase and block JAK/STAT pathway, thus participating in many important biological processes such as cell proliferation, differentiation, apoptosis and immune regulation.