REVIEW ARTICLE

RHEUMATOID ARTHRITIS THERAPIES: PRESENT AND FUTURE

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by inflammation of synovium, cartilage damage and co-occurring of various other disorders. Significant improvement has been achieved in RA therapeutics in last two decades. However, newer, more efficient and more cost-effective therapeutic applications are still needed to be developed. Current therapies in RA are mostly acting to restrict inflammation. Non steroidal anti inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs) are conventionally used in RA therapy. Studies showed higher efficacy of anticytokine therapy such as anti-IL-6 and anti-TNF. Rituximab, targeting B cells, after establishing its potential was approved to be used in combination with methotrexate in 2006. Abatacept, CLTA-4-IgG1, has been developed to block CD28 and CD80 or CD86 interaction leading to the termination T cell activation. Molecular inhibitors are relatively new in RA therapeutics such as tocilizumab, tofacitinib and baricitinib. FDA has approved tofacitinib to be used as a treatment for moderate and severe RA. Future holds promising therapeutic options based on numerous studies. IL-12, IL-17 and IL-23 are the targets of future anticytokine therapies. Several lymphocyte targeting agents including ofatumumab, ocrelizumab and veltuzumab have been developed and are currently in phase II and phase III clinical trials. There is a vast range of potential targets in RA enabling us to expand the therapeutic options over the next decade.

Keywords: Anakinra, DMARDs, NSAIDs, Rheumatoid arthritis, Tocilizumab.

INTRODUCTION

Rheumatoid arthritis (RA) is a disease manifested by inflammation of synovial membrane, articular cartilage damage and co-occurring of various other disorders, including problems in the bone, vasculature, brain and lungs. The last two decades have witnessed significant improvement in the therapy of RA[1]. Anti-inflammatory drugs, both steroids and non-steroidal, introduced around mid-20th century into the therapy of RA lead to symptomatic improvement and pain relief. However, there were some significant side effects but major problem with them was that they were just unable to halt disease progression. With the identification of the beneficial effects of aminopterin antimetabolite, chemotherapeutic agents known as disease-modifying anti-rheumatic drugs (DMARDs) were introduced to RA therapeutics in late 1980s. The major advantage of DMARDs e.g. methotrexate was significant delay in the disease progression. Although methotrexate is current first line therapy in inflammatory rheumatic diseases, cytotoxicity and partial efficacy are its limiting factors[1].

An important factor in RA treatment is its early and timely diagnosis i.e. sooner the therapy begins, the more effective will be its response. Current therapies for RA are mainly targeting to restrict inflammation[2]. Traditionally, these approaches were based on agents that helps in reduction of disease symptoms. However, in past 20 years significant advances led to a whole new generation of therapies that are involved in blockade of certain cytokines and immune regulators. With the increasing knowledge and better understanding of inflammation contribution to the disease initiation and progression, these therapies, known as biologic agents, have been developed.

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Conventional Therapy for RA

Pharmaceutical compounds of diverse chemical nature formed the basis of RA therapy. From the discovery of aspirin, the non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used in RA therapies, supported later by discovery of cyclooxygenase 2 (COX-2)-selective agents. These agents did not achieve true success because they show symptomatic improvement but were unable to cause any hindrance in the joint destruction[3]. Furthermore, gastric and renal toxicity is limiting factor of NSAIDs. Because of involvement of glucocorticoid receptor in diverse functions, Glucocorticoids mark the most important advancement in RA therapy having potential anti-inflammatory effects. However, they are also associated with many diverse effects that limit their long term usage. The widely used therapeutics in RA are the conventional DMARDs including methotrexate, hydroxy-chloroquine, azathioprine and sulphasalazine. Their exact mechanism of action remains unclear[4]. DMARD includes TNF-blocking agents that may be neutralizing anti-TNF monoclonal antibodies, the polyethylene glycol–linked mAb or the soluble TNF receptor 2–IgG-Fc fusion protein. Other DMARDs that have FDA approval includes interleukin 6 receptor (IL-6R) blocking monoclonal antibody (tocilizumab), the IL 1 receptor antagonist (anakinra), the anti-CD20 B cell depleting monoclonal antibody (rituximab) and the T cell activation inhibitor (abatacept). Similarly, alternative IL 6 blocking strategies, anti-IL 17 monoclonal antibodies (secukinumab and ixekizumab) and the IL 17 receptor-blocking monoclonal antibody (brodalumab) are under development and clinical trials. Moreover, Janus Kinase (JAK) inhibitor (tofacitinib) was approved as a treatment option for RA in 2012[5].

Anti-cytokine Therapies

It is a well-known fact now that inflammatory cytokines play a vital role in RA pathogenesis by coordination of joints pathology symptoms[6]. Cytokines including IL-23, IL-18, IL-17 and IL-12 regulate local inflammation and Il-6, IL-1β and TNF are involved in regulation of homeostatic processes along their classical role in inflammation[6]. Their involvement in inflammation established them as primary targets in RA and proved to be the basis for production of TNF blockers including etanercept, anti-IL-6R (tocilizumab) and anti-IL-1β (anakinra)[7].

Anakinra is provedless effective in RA while it has considerable efficacy in other diseases which are associated with inflammation like gout[8]. While biologic agents employed targeting IL-6 or TNF are more effective in RA than other inflammatory diseases. Tocilizumab was witnessed effective in a clinical trial consisting 56 patients of idiopathic arthritis[8]. TNF and IL-6 are linked to regulate extracellular matrix degradation, bone erosion, osteoclastogenesis and leukocyte activation[9]. TNF mainly functions through downstream signaling via the nuclear factor κB (NFκB) and extracellular signal-regulated kinase (ERK)[9]. While signal transducer and activator of transcription 3 (STAT3) and to little extent STAT1 are used by IL-6 to function[10]. Increased levels of STAT3 have been observed in synovial tissues of RA patients and its involvement in synovial hyperplasia and inflammatory mediator's regulation establishes its role in chronic progression of the disease[10]. However, these pathways are not solely followed by IL-6 and TNF as certain other cytokines function through NFκB including IL-17 and IL-1β or STAT3 including IL-23, IL-21, IL-10[11].

Lymphocyte Targeting

B cells and T cells actively participate in autoimmune disease progression via certain mechanisms including auto-reactive antibody generation and the differentiation of memory cells into effector cells with proinflammatory cytokine signatures. Rituximab and abatacept are currently being used clinically to target cells[12]. Rituximab is the most successful antibody targeting B cells via CD20 that is expressed by mature B cells as well as pre-B cells but not by antibody secreting plasma cells[13]. Its mechanism of action has been proposed through various

models namely antigen dependent cellular cytotoxicity, complement-dependent cytotoxicity and induction of apoptotic cell death[14]. B cell depletion cannot be directly associated to therapeutic efficacy in RA because B cells were depleted in all the treated patients but clinical response was observed in only 60% of them[14]. Rituximab was approved to be used in combination with methotrexate as a RA treatment option in 2006[13].

T-cell are activated through two signals i.e. MHC associated antigen presentation and interaction of co-stimulatory molecules particularly T-cell surface specific glycoprotein CD28 with T-cell activation antigens CD80 and CD86 that are expressed on antigen presenting cells[15]. CTLA-4 functions as T-cell suppressor and is known to be key regulator in peripheral T-cell tolerance. Abatacept is CLTA-4-IgG1 that is developed to stop the CD28 interaction with CD80 or CD86 terminating T cell activation[16]. Abatacept is the only approved T cell targeting therapy for RA but its mode of action remains ambiguous. It is shown to inhibit interactions of T cells and synovial fibroblasts in an ex vivo study on RA patients and healthy control samples[16]. Co-stimulation blockade is associated with T-cell anergy and tolerance in animal models of autoimmune disorders indicating towards treatment free remission. However, these results are not yet reported in any clinical study on humans[15].

Small-molecule Inhibitors

An oral treatment option for inflammatory disorders including RA, psoriasis a class of DMARDs is developed[17]. Tofacitinib, a JAK inhibitor, is the most advanced among these drugs. JAK family kinases including JAK1, JAK2, Tyk2, and JAK3 play vital roles in homeostasis and immune responses. Tofacitinib mainly inhibits JAK1 and JAK3 and to some extent JAK2. Baricitinib, another molecular inhibitor, targets JAK1 and JAK2[17,18]. FDA has approved tofacitinib to be used as a treatment for moderate and severe RA. Neutropenia, hepatic steatosis and elevated levels of lipids, alanine transaminase (ALT), aspartate transaminase (AST) and bilirubin indicating liver damage are some of the observed adverse effects of tocilizumab, tofacitinib and baricitinib[18].

Future of RA Therapeutics

Future of Anticytokine Therapies

Currently, tocilizumab is the only IL-6 inhibitor being used in RA management. Its efficacy laid the foundation for development of similar drugs against various domains and receptors od IL-6[19]. Anti-cytokines under development including olokizumab, sirukumab, sarilumab and BMS94542940 blocks classical IL-6R signalling as well as IL-6 trans-signalling[20]. There are also some Anti-cytokines that specifically blockIL-6 trans-signalling[21]. Biologic agents against IL-12, IL-23 and IL-17 such as briakinumab, ustekinumab and brodalumab respectively are being developed[22]. Hetero-dimeric cytokines such as IL-12 and IL-23 are therapeutic target of interest[23]. IL-12 and IL-23 play role in development and maintenance of TH1 and TH17 cells respectively. In IL-17A receptor gene knockout and IL-23 deficient mice models of RA, disease was diminished[23]. These studies indicate their potentials as therapeutic agents. In clinical trials their efficacy will be compared to currently available anticytokine therapeutics.

Future of Lymphocyte Targeting

Following rituximab's success, anti–CD20 depleting antibodies such as ofatumumab, ocrelizumab and veltuzumab were developed and are currently in phase II and phase III clinical trials[24-25]. Results of these trials are not yet published or released. Other B cell targeting agents include epratuzumab that targets CD22 is developed and being studied for its potential in autoimmune disorders. The efficacy of these new therapeutics are currently under study. Other agents are developed against B-cell activating factor (BAFF) and TNF ligand superfamily members such as belimumab and atacicept. Phase III clinical trials were carried out[26,27]. Atacicept

didn't show any significant efficacy in clinical trials in a study of over 500 patients. Belimumab showed promising results in phase III clinical trials in systemic lupus erythematosus but its role in RA is not reported[28]. Therapeutic potentials of non-mitogenic anti-CD3 monoclonal antibody modulating T-cell responses were proposed in RA but have not been studied or reported further[29].

DISCUSSION

Recent therapeutic developments over the past two decades have revolutionized the RA therapy. These developments can be divided into three classes including Anti-cytokines, targeting lymphocytes and molecular inhibitors of signaling pathways involved in the pathogenesis of RA. The benefits and adverse effects associated to each class are different. Most of the research is carried out in the area of developing Anti-cytokines and molecular inhibitors. Moreover, there is strong evidence of targeting lymphocytes as a potential therapy as well. These therapies can also be experimented and evaluated to be used in combination with each other. With the knowledge and success of current therapies, the research is now to be carried out towards the strategies to assure disease remission in RA patients. Oral therapeutics is an emerging area of research with the approval of tafacitinib usage in RA. There is a range of signaling pathways involved in RA pathogenesis enabling us to expand the therapeutic options over the next decade.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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