

Advances in the treatment of rheumatoid arthritis

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Abstract

The intense pursuit of novel therapies in rheumatoid arthritis has provided physicians with an assorted set of biologic drugs to treat patients with moderate to severe disease activity. Nine different biologic therapies are currently available: seven inhibitors of pro-inflammatory cytokines (five targeting tumor necrosis factor [TNF], one interleukin [IL]-1 and one IL-6), as well as a T- and a B-lymphocyte targeting agent. All these drugs have roughly similar efficacy profiles and are approved as first- or second-line therapy in patients who failed to respond to conventional disease-modifying anti-rheumatic drugs (DMARDs) and in most cases for first line use in rheumatoid arthritis as well. Despite the irrefutable clinical and radiological benefits of biologic therapies, there are still low rates of patients achieving stable remission. Therefore, the quest for new and more effective biologic therapies continues and every year new drugs are tested. Simultaneously, optimal use of established agents is being studied in different ways. Recently, the approval of the first small molecule targeting intracellular pathways has opened a new chapter in the treatment of rheumatoid arthritis. Other emerging treatment strategies include the activation of regulatory T cells as well as new cytokine-targeting therapies.

Introduction

Rheumatoid arthritis is an autoimmune disease affecting approximately 1% of people in the developed world [1]. It is characterized by synovial inflammation and joint destruction, eventually inducing severe disability, if left untreated [2].

The international recommendations for the treatment of rheumatoid arthritis include DMARDs such as methotrexate as the main treatment approach, while biologic DMARDs are usually considered only when the former are not sufficiently effective [3].

Here, we provide an overview of currently available as well as emerging immunomodulatory therapies, biologic (Table 1) and targeted synthetic DMARDs, in rheumatoid arthritis. Such therapeutic strategies either target pro-inflammatory cellular products (cytokines), cellular receptors (cluster of differentiation or [CD] molecules)

or intra-cellular pathways leading to the expression of pro-inflammatory molecules.

Cytokine-targeting agents

Etanercept

Etanercept, the first TNF inhibitor approved in 1998 for the use in rheumatoid arthritis, is a recombinant fusion protein, which links the soluble TNF receptor to the Fc portion of human Immunoglobulin G (IgG). It works as a decoy receptor, binding to soluble TNF and blocking the binding to its receptor. It has a short half-life (3-6 days), and is usually administered subcutaneously 50 mg once a week or 25 mg twice a week. The clinical efficacy of etanercept has been shown both as monotherapy [4] and in combination with methotrexate [5], the combination providing better results than methotrexate or etanercept alone [6].

Several recent studies have suggested that in patients with established rheumatoid arthritis who have achieved

Table 1. Overview of the currently available biologic DMARDs for the treatment of rheumatoid arthritis

Name	Target	Format	Mechanism	Administration	Approximate half-life*
Etanercept	TNF	Recombinant human fusion protein of the TNF receptor and the Fc portion of IgG1.	Works as a decoy receptor. It binds to soluble TNF, blocking the binding to its receptor	sc. injection once (50 mg), or twice (25 mg) a week	3-6 days
Adalimumab	TNF	Fully human IgG1 MAb	Binding to TNF	sc. injection once every second week	13 days
Infliximab	TNF	Chimeric murine-human IgG1 MAb	Binding to soluble and mb bound TNF	iv. infusion every 4-8 weeks	9 days
Golimumab	TNF	Fully human IgG1 MAb	Binding to soluble and mb bound TNF	sc. injection once a month or iv. Infusion at 0 and 4 weeks, thereafter every 8 weeks	13 days
Certolizumab-pegol	TNF	Humanized pegylated anti-TNF Fab' fragment	Binding to TNF	sc. injection once every second week	14 days
Anakinra	IL-1	Recombinant human IL-1 receptor antagonist	Binding to IL-1 type-I receptor	sc. injection once a day	4-6 hours
Tocilizumab	IL-6	Humanized recombinant IgG1 MAb	Binding to soluble and membrane bound IL-6 receptor	iv. infusion every 4 weeks	10-13 days
Rituximab	B cells	Chimeric murine-human IgG1 MAb	Binding to CD20 and depletion of CD20+ B cells	Two initial infusions 14 days apart. Courses may be repeated every 6 months or more frequently depending on disease activity	18 days (range: 5-76 days)
Abatacept	T cells	Recombinant human fusion protein of the extracellular domain of CTLA-4 and the Fc portion of IgG1	Binding to CD80/ CD86, blocking T-cell co-stimulation	iv. infusion every 4 weeks or sc. injection once a week	13 days (range: 8-25 days)

CTLA-4, cytotoxic T lymphocyte associated antigen 4; DMARDs, disease-modifying anti-rheumatic drugs; IgG, immunoglobulin G; IL, interleukin; iv, intravenous; MAb, monoclonal antibody; mb, membrane; sc, subcutaneous; TNF, tumor necrosis factor

*The half-lives provided here refer to the biological effect and the physical half-life reported by the manufacturers which may differ depending on the format of the drug.

a long-lasting low disease activity state on the combination of methotrexate plus etanercept, the latter drug can in many cases be continued at half the usual dose [7,8] or at more sparse treatment intervals [9].

Adalimumab

Adalimumab is the first fully human monoclonal antibody binding TNF. It is administered subcutaneously and has a longer half-life than etanercept (approximately 13 days), allowing a less frequent injection interval (every second week). The clinical efficacy of adalimumab in combination with methotrexate was shown in patients with early aggressive rheumatoid arthritis [10] as well as in patients who had previously failed to respond to other biologic or non-biologic DMARDs [11,12]. A recent study evaluated the use of methotrexate + adalimumab as first-line treatment for patients with early rheumatoid arthritis, with a unique trial design that re-randomized patients who had achieved a low disease activity state with the combination after 24 weeks [13]. After 76 weeks, around 90% of patients who continued on both (*versus* around 80% of patients who continued with only methotrexate) had maintained low disease activity (disease activity score [DAS]28>3.2). While this difference was statistically significant, the most important conclusion might well be that, for at least a subset of patients with early rheumatoid

arthritis, induction-maintenance is a highly successful therapeutic strategy with an obviously favorable health-economic profile.

Infliximab

Infliximab is a chimeric murine/human IgG1 monoclonal antibody, also directed against TNF (soluble and membrane bound), usually administered intravenously every 4-8 weeks. Ensuing randomized controlled trials showed that infliximab in combination with methotrexate produced a rapid reduction of signs and symptoms, reduced radiographically measured disease progression and improved physical function [14-16]. In addition, the reduced radiographic progression was shown to be independent of clinical response [14,17].

Golimumab

Golimumab is a human monoclonal antibody, binding to both soluble and membrane bound TNF. It has a half-life of approximately 13 days and is administered subcutaneously once a month. Recently, the Food and Drug Administration (FDA) approved an intravenous format of this drug for the treatment of rheumatoid arthritis, to be administered at 0 and 4 weeks, thereafter every 8 weeks. Golimumab has been shown to be effective in the treatment of moderate to severe rheumatoid

arthritis patients who failed to respond or were naïve to methotrexate, as well as in patients who failed to respond to at least one anti-TNF therapy [18-20].

Certolizumab pegol

Certolizumab pegol is a pegylated, humanized anti-TNF Fab fragment. Since it lacks the Fc portion, it does not induce apoptosis through complement activation or antibody-dependent cell-mediated cytotoxicity (ADCC). The pegylation process (addition of polyethylene glycol) delays the elimination of this small antibody-derived protein, prolonging its half-life (approximately 14 days). Certolizumab is administered subcutaneously every second week. A study with a wider inclusion and fewer restrictions than most studies, named REALISTIC [21], confirmed the clinical benefit and overall safety and tolerability of this agent in a broad population of rheumatoid arthritis patients. Likewise, the CERTAIN trial [22] demonstrated that patients with moderately active rheumatoid arthritis may also benefit from this TNF-inhibitor.

Anakinra

Anakinra, a recombinant human IL-1 receptor antagonist, has a very short half-life (4-6 hours) and must be administered subcutaneously once a day. Due to this inconvenience, as well as indirect comparative reports showing limited success of anakinra in rheumatoid arthritis compared to TNF inhibitors [23-25], this drug is not commonly used in adult rheumatoid arthritis. Nevertheless, anakinra has been successfully used in juvenile rheumatoid arthritis and other autoinflammatory disorders [26-28].

Tocilizumab

Tocilizumab is a humanized recombinant IgG1 monoclonal antibody that binds to soluble and membrane bound IL-6 receptor. It has a half-life of 10-13 days and is administered intravenously every 4 weeks. A subcutaneous formulation of tocilizumab has been developed and was very recently approved in the United States. Tocilizumab (162 mg) injected subcutaneously once weekly has recently shown a comparable efficacy and safety profile to TCZ-IV (8 mg/kg) [29,30]. Tocilizumab has proven effectiveness for the treatment of rheumatoid arthritis after inadequate response to conventional DMARDs [31] and also the treatment of rheumatoid arthritis refractory to anti-TNF therapy [32]. In the ADACTA trial [33], tocilizumab monotherapy was superior to adalimumab monotherapy.

Cell-targeting agents (B and T lymphocytes)

Rituximab

Rituximab is a chimeric murine/human monoclonal antibody directed against CD20, an antigen expressed by

B cells at different stages of differentiation (pre-B cell to mature stages) but not by haematopoietic stem cells or plasma cells. It induces the depletion of B cells, which are involved in the production of autoantibodies as well as in the induction of T cell activation and production of pro-inflammatory cytokines [34]. This biologic was approved originally for the treatment of non-Hodgkin lymphoma and then approved in 2006 as a second-line therapy (after failure of anti-TNF therapy) in patients with moderate to severe rheumatoid arthritis. Its efficacy has been shown in patients who failed to respond to methotrexate or to one or more anti-TNF therapies [35,36] after a single course of two infusions of rituximab. One study in rheumatoid arthritis patients (with inadequate response to a previous anti-TNF agent) suggested a relative benefit of rituximab over alternative anti-TNF agents on disease activity, but found a similar rate of radiographic erosion progression between the two treatments [37]. In addition, the presence of autoantibodies appears to favor clinical responses to rituximab, as indicated by studies showing a better effect among seropositive rheumatoid arthritis patients compared to seronegative rheumatoid arthritis patients [38-40]. The effectiveness of rituximab was also reported in a refractory group of rheumatoid arthritis patients with long disease duration. Moreover, it appeared to be relatively safe in a population with high prevalence of comorbidities, including malignancy and recurrent infections [41].

Abatacept

Abatacept has been approved for the treatment of patients with moderate to severe rheumatoid arthritis who have had an inadequate response to one or more conventional or biologic DMARDs. It is a fully human fusion protein comprising the extracellular domain of cytotoxic T lymphocyte associated antigen-4 (CTLA-4) linked to the Fc portion of human IgG.

The antigen-specific interaction between antigen presenting cells (APCs) and T cells is normally accompanied by the binding of a ligand on the APC (CD80 or CD86) to the co-stimulatory receptor on T cells (CD28). This interaction is called co-stimulation and results in an effective T cell activation characterized by proliferation and production of inflammatory cytokines (IL-2, TNF). The inhibitory antigen CTLA-4 binds also to CD80 and CD86, though with a higher affinity than CD28 and with an inhibitory effect. Abatacept prevents T cell co-stimulation by binding, with its CTLA-4 portion, to CD80 and CD86, blocking in this way CD28-mediated T cell activation.

Abatacept is administered in infusions (once every 4 weeks) or subcutaneously (once every week). Both treatment options showed comparable efficacy and safety in patients

with inadequate response to methotrexate [42]. A recent head-to-head trial comparing abatacept and adalimumab (both combined with methotrexate) displayed nearly identical efficacy, with some safety outcomes favoring abatacept [43,44].

Inhibitor of intracellular signaling pathways

Tofacitinib

Tofacitinib, a new non-biologic agent, is the first Janus kinase (JAK) inhibitor approved by the FDA as well as regulatory agencies in various other countries (Japan, Switzerland, Russia, Argentina, Kuwait and The United Arab Emirates) for the treatment of rheumatoid arthritis. In contrast, the European Medicines Agency did not approve this drug. JAK enzymes are a group of four cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3 and TYK. These enzymes bind to the intracellular portion of various cytokine receptors and, upon stimulation of the tyrosine kinase-associated receptor, they transmit the signal from the cell surface into the nucleus by phosphorylation and activation of signal transducer and activator of transcription (STAT) molecules. JAKs are involved in the differentiation and activation of lymphocytes as well as in the secretion of proinflammatory cytokines. A number of cytokines known to be relevant in rheumatoid arthritis pathophysiology (such as IL-2, IL-4, IL-6, IL-7, IL-9, IL-15 and IL-21) are regulated by JAK-dependent pathways. Tofacitinib is an inhibitor of Janus kinase 1 and 3 (with much lower affinity for JAK2 and TYK) [45]. Tofacitinib is administered orally and the recommended dose is 5 mg twice daily. It can be used as monotherapy or in combination with methotrexate or other sDMARDs (synthetic DMARDs – sulfasalazine, leflunomide or hydroxychloroquine) to treat moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to methotrexate. The clinical efficacy of tofacitinib was shown to be very similar to the anti-TNF agent adalimumab [46].

Major safety issues with biological and targeted synthetic DMARDs

Safety concerns common to all anti-rheumatic therapies include an increased risk for viral and bacterial infections [47]. Patients on anti-TNFs have a higher risk of tuberculosis (TB) reactivation and therefore TB screening before treatment initiation is compulsory. Anti-TNF treatment has also been associated with an increased risk of herpes zoster. Infliximab was associated with a significantly higher risk of patient withdrawals due to adverse events compared to controls and to other anti-TNFs. Anti-TNFs do not appear to increase the risk of malignancies in general; earlier reports of an increased risk of lymphoma or non-melanoma skin cancer were

not confirmed in later and larger studies [48,49]. A recent study from the Swedish registry showed a slightly increased risk of melanoma in rheumatoid arthritis patients treated with anti-TNF agents [50].

SWITCH-RA, a prospective observational study, showed an overall similar incidence of adverse events in patients, non-responsive or intolerant to a single anti-TNF agent, who switched to rituximab or to a second anti-TNF [51]. However, reports suggested an increased risk (1 case per 25,000 individuals) of progressive multifocal leukoencephalopathy due to reactivation of John Cunningham (JC) virus in rheumatoid arthritis patients treated with rituximab [52,53]. Although this is a rare adverse event associated with rituximab therapy in rheumatoid arthritis patients, the devastating nature of progressive multifocal leukoencephalopathy advocates for sustained vigilance in this group of patients.

According to data from randomized controlled trials and observational studies, the main safety risk for patients receiving abatacept is infection [54]. A head-to-head comparison of abatacept versus adalimumab showed similar safety profiles and fewer injection site reactions with abatacept [55].

Tocilizumab has a distinct safety profile. Although clinical events (including infections and malignancies) occur at comparable rates to anti-TNF agents, there are more instances of abnormal laboratory tests on follow-up, including elevated liver enzymes, cytopenias, and lipid elevations. In addition, inhibition of IL-6 by tocilizumab prevents the production of C-reactive protein (CRP) in response to inflammation. A few case reports of tocilizumab-treated patients with moderate to severe bacterial infections, and normal CRP support the idea that CRP may not be used as a marker in case of infection [56-58]. Reports on the incidences of herpes zoster (multidermatomal or ophthalmic) with tocilizumab [59,60] indicate an increased risk for this serious infection in tocilizumab-treated patients. If this risk were confirmed, systematic vaccination against varicella-zoster virus or antiviral long-term prophylaxis may be considered.

Overall safety of tofacitinib in the clinical trials was acceptable, with infection rates similar to biologics [61]. A number of laboratory abnormalities and an increased incidence of infections (including herpes zoster) were seen, not unlike those described above with the anti-IL6 agent tocilizumab and, indeed, IL-6 signaling is dependent on JAK1 and 2 [62]. The ORAL Standard trial, a phase 3 study, compared the efficacy and safety of tofacitinib and of the anti-TNF agent adalimumab to placebo, showing similar efficacy for the active compounds *versus* placebo,

with an increased rate of serious infections in the tofacitinib group [46]. Larger trials of longer duration are necessary to assess the risk of infections and other adverse events associated with tofacitinib and to compare the safety of this drug with that of the other available treatments for rheumatoid arthritis.

Biosimilar agents

The patents for many biological agents are going to expire in the coming years, and this has triggered major interest in the development of “biosimilars” by several companies. The advent of these potentially less expensive alternatives could make the treatment of rheumatoid arthritis more cost-effective, and might afford access to biologics to a greater number of rheumatoid arthritis patients worldwide. However, biosimilars cannot be identical to the original biologics, due in part to stochastic variability in post-translational modifications to the molecules, and in part to potential differences in the manufacturing conditions. These differences have raised some concerns regarding the efficacy, immunogenicity and safety profile of the intended copies. As a consequence, the registration and approval process for biosimilars is considerably more demanding than for pharmaceutical generics (but less so than for completely new drugs). As the production costs for biosimilars will not be different from biologics, they will still remain costly, and the savings compared to original biologics may be relatively modest. The status of development as well as regulatory issues related to the approval of biosimilar agents in the world has been reviewed in a recent publication by Scheinberg and Kay [63].

New anti-rheumatic agents in the pipeline

Emerging cytokine-targeting therapies include anti-IL-17 and anti-IL-15. Serum IL-17A levels and, to a greater extent, synovial fluid IL-17A levels are elevated in many patients with rheumatoid arthritis, which is associated with cartilage and bone degradation. The anti-IL-17A monoclonal antibodies secukinumab and ixekizumab, and the anti-IL-17 receptor subunit A monoclonal antibody brodalumab have been evaluated in phase II clinical trials. Of these, secukinumab is the furthest advanced, with phase III trials ongoing in patients who had inadequate response to a previous TNF-blocker therapy [64]. Clinical benefit in disease activity was also observed in a phase I/II trial where patients with active rheumatoid arthritis received anti-IL-15 as monotherapy [65]. Another cytokine that has been found to play a role in the pathogenesis of rheumatoid arthritis is IL-20. This cytokine is increased in the synovium of patients with rheumatoid arthritis. NNC0109-0012, a human recombinant IgG4 that binds and neutralizes IL-20, is now in phase II trials. A double-blind study has shown promising results, with clear improvements of disease activity scores, physical function

and pain, particularly in seropositive rheumatoid arthritis patients [66].

Among cell-receptor targeting therapies, there have recently been studies of the non-depleting antibody BT-061 (tregalizumab) that is thought to act by activating T regulatory cells, which have been found to malfunction in autoimmune diseases such as psoriasis and rheumatoid arthritis. Since only natural regulatory mechanisms would be activated by BT-061, it is expected that it would be safer than other available therapies as the immune system remains mainly functional to fight infections. The TREAT 2b is a phase IIb study investigating the safety and efficacy of tregalizumab in combination with methotrexate in the treatment of subjects with active rheumatoid arthritis who have had an inadequate response to methotrexate [67,68].

Due to the success of JAK inhibition, several JAK inhibitors are currently being tested at different stages of development, including baricitinib, a JAK1/2 inhibitor [69,70], and VX-509, a JAK3 inhibitor [71], which produce a clinical improvement superior to placebo.

Other intracellular molecules that were considered suitable therapeutic targets due to their role in the transduction of inflammatory signals, including the spleen tyrosine kinase (SYK) and the mitogen-activated protein (MAP) p38 kinases, led to the development of new classes of drugs evaluated in rheumatoid arthritis clinical trials that were subsequently abandoned due to lack of efficacy [72].

Conclusions and future perspectives

The discovery and targeting of new relevant pathways in the pathogenesis of rheumatoid arthritis have provided a greater possibility of controlling this disease, although more knowledge is required in order to better allocate suitable therapy to our patients. It is widely accepted that the initiation of biologic treatment should be reserved for patients who have failed to respond to at least one DMARD, most often methotrexate. Yet, greater efforts should be put into the optimization of the usage of the existing drugs.

It is known that the main advantage of biologics when compared to DMARDs is a more rapid effect, as well as prevention of radiographic progression. Given the benefits of aggressive and early treatment in the long run, there is consequently a lot of interest at the moment in finding out whether such early aggressive treatment should include biologics.

At present, the limited data that are available from head-to-head clinical trials do not strongly support the use of one agent over another. At this time, we are participating

in a large Nordic investigator-initiated clinical trial, NORDSTAR, where initial conventional therapy is compared directly to anti-TNF with certolizumab, abatacept, or anti-IL6.

The ultimate goal in rheumatoid arthritis is to achieve remission, which could be accomplished through a personalized treatment that provides the right drug at the right dose for the adequate length of time, improving outcomes and minimizing side effects.

Clinicians still lack reliable tools to predict which patients are more likely to respond to a given biologic. In this respect, biomarkers are promising tools. The availability of biomarker scores offers the possibility of improving the clinical assessment of disease activity as a decision-helping tool in rheumatoid arthritis management [73,74].

It would be advantageous to be able to predict not only whether patients will respond to a given biologic but also whether continuation will be needed once treatment target has been achieved. Therefore, studies dealing with tapering or stopping therapy as well as predictors of response to therapy are of enormous relevance in the future.

In summary, the development of biologic therapies has greatly advanced the field of rheumatoid arthritis therapeutics; trials of additional biologics, the burgeoning development of small molecular compounds with comparable efficacy, and the optimization of therapeutic strategies using all available classes of agents will lead to ever more impressive improvements in the results achieved for our patients.



Abbreviations

APC, antigen presenting cell; CRP, C-reactive protein; CTLA-4, cytotoxic T lymphocyte associated antigen-4; DMARD, disease-modifying anti-rheumatic drug; FDA, Food and Drug Administration; IgG, immunoglobulin G; IL, interleukin; JAK, Janus kinase; TNF, tumor necrosis factor; TB, tuberculosis.

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