Prospective new biological therapies for rheumatoid arthritis

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Abstract

Advances in the current knowledge of pathogenetic mechanisms of rheumatoid arthritis have contributed to the development of biological therapy, and translated research findings into clinical practice. TNF-α (infliximab, etanercept, adalimumab), IL-1 (anakinra) and IL-6 (tocilizumab) inhibitors, a B-cell depleting agent (rituximab) and a drug blocking T-cell costimulation (abatacept) have been approved for rheumatoid arthritis. The progress in manufacturing biotechnology has contributed to the development of several other prospective agents that may form the basis for the therapy of rheumatoid arthritis in the near future. New or modified TNF-α inhibitors (golimumab, certolizumab pegol), new monoclonal antibodies against other cytokines (e.g. IL-1, IL-6, IL-12, IL-15, IL-17, IL-23), and other agents targeting B-cell depletion (e.g. ocrelizumab, ofatumumab) are in various stages of development. Many pharmaceutical companies have focused on developing small molecule inhibitors with possible peroral administration, which are considered promising drugs for rheumatoid arthritis. In most cases, these small molecules inhibit cellular kinases (e.g. p38, JAK or Syk) that mediate the signaling and transcription of proinflammatory genes. In this review, we describe the cytokine inhibitors and modulators of the immune response currently in ongoing clinical trials, the results of which may further expand the spectrum of efficient therapies for chronic autoimmune diseases.

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ARTICLE INFO

Article history:
Received 1 March 2009
Accepted 17 March 2009
Available online 26 March 2009

Keywords:
Rheumatoid arthritis
Biological therapy
Clinical trials
Monoclonal antibodies
Small molecules

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1. Introduction

Biological therapy has become a cornerstone in the treatment of rheumatoid arthritis (RA) with inadequate response to standard disease modifying antirheumatic drugs (DMARDs). Currently, seven approved biological agents are available (Table 1). Biological therapy targeting molecules and cells specific for processes associated with the pathogenesis of RA is very efficient yet still unable to induce remission or even cure in most patients. Expanding spectrum of potential therapies is currently being tested in various stages of clinical trials that have been facilitated by recent understandings regarding the pathogenesis of RA. The aim of this report is to review potential new therapeutic concepts, which may be promising for patients with RA.

2. Prospective biological agents

Pharmaceutical companies aim to modify existing agents or develop further biological therapeutics and treatment strategies in order to reduce the costs of manufacturing technology, as well as to improve the clinical efficacy and perhaps even induce total remission of the disease. The most promising agents currently being tested in various stages of clinical trials are summarized in Table 2. Biological agents can be divided into monoclonal antibodies and small molecules [1,2].

2.1. Monoclonal antibodies

The use of monoclonal antibody therapy in rheumatology has increased in recent years [1]. Initially, these treatments consisted of chimeric antibodies with human constant regions of light and heavy chain and the variable murine binding site for the target molecule. Progress in manufacturing technology led to a reduction of immunogenicity, and humanized and eventually fully human antibodies were created. These antibodies function by neutralizing a target cytokine or its receptor, blocking costimulation molecules, and inducing cytolysis, apoptosis or depletion of target cell molecules.

2.1.1. TNF-α inhibitors

Two additional TNF-α blocking agents are likely to be approved in 2009 for the treatment of RA. Preliminary data of subcutaneously administered golimumab (CNTO148), a fully human monoclonal anti-TNF-α antibody and certolizumab pegol (Cimzia), a humanized monoclonal anti-TNF-α antibody exhibit the same efficacy and spectrum of adverse events as currently available TNF-α inhibitors [3,4].

2.1.2. IL-1 inhibitors

To simplify the dosing, decrease the risks of local adverse events, increase the affinity to IL-1, and thus improve the efficacy compared to anakinra, a humanized monoclonal antibody targeting IL-1, canakinumab (ACZ885), has been recently developed. The preliminary results of clinical trials in patients with systemic juvenile idiopathic arthritis are promising [5], and a phase II clinical trial in patients with RA began in 2008 (http://clinicaltrials.gov).

2.1.3. IL-6 inhibitors

Tocilizumab is a humanized monoclonal antibody against IL-6 receptor. The results of several phase III clinical trials suggest tocilizumab as an agent with extreme potential for the treatment of active RA [6]. As of 2009, the European Medicines Agency (EMEA) described a favorable benefit-to-risk balance for tocilizumab in combination with MTX, and approved this indication for the treatment of moderate to severe active RA in adult patients who have either responded inadequately or were intolerant to previous therapy with one or more DMARDs or TNF-α inhibitors (http://www.emea.europa.eu). In 2008, a phase II clinical trial of a subcutaneously administered monoclonal antibody against IL-6 (CNTO 136) was initiated to establish the suitable dosage, and confirm the efficacy and safety of the drug (http://clinicaltrials.gov).

2.1.4. IL-15 inhibitor

Blocking IL-15 in an experimental model of arthritis led to a significant reduction of cartilage and bone destruction. The first open, placebo-controlled, double blind study proved the humanized monoclonal antibody against IL-15 (HuMax-IL-15) to be efficient [7], however, a phase II clinical trial of a fully human monoclonal antibody against IL-15 (AMG 714) failed to confirm significant efficacy. Other cytokines, such as IL-2, IL-4, IL-7, IL-9 and IL-21, share an identical receptor subunit of the γ chain and thus some functions of IL-15. So far, no data is available on the use of these cytokines as a therapeutic target in RA patients.

2.1.5. IL-17 inhibitor

Th17 cells, a subset of memory T-cells that play a key role in an autoimmune inflammation, are a major source of IL-17. IL-17 increases production of several proinflammatory cytokines such as IL-1, IL-6, or TNF-α and regulates osteoclastogenesis. Inhibition of IL-17 generated successful results in the treatment of an experimental arthritis model [8]. A phase I/II clinical trial of a monoclonal antibody against IL-17 (AIN457) in patients with RA is currently in progress (http://clinicaltrials.gov).

2.1.6. IL-12/IL-23 inhibitor

IL-12 is a key inducer of Th1 polarization and IL-23 is responsible for the proliferation of a Th17 subset of memory T-cells [9]. A recent clinical trial evaluating the effect of a specific monoclonal antibody, ustekinumab, against the p40 subunit of cytokines IL-12 and IL-23 in patients with psoriasis has generated promising results [10]. On an experimental level, a positive effect of an IL-23 blocking antibody was described in collagen-induced arthritis [11] and one proof-of-concept study has shown that besides associated psoriatic skin lesions, ustekinumab treatment can also reduce the signs and symptoms of arthritis in patients with psoriatic arthritis [12]. Recently initiated clinical trials could show if ustekinumab is of any practical use in the treatment of RA (http://clinicaltrials.gov).

2.1.7. Inhibitors of the TNF superfamily members

The results of a phase II clinical trials of baminercept (BC9924), an inhibitor of LT-β (lymphotoxin-β), and belimumab, a fully human monoclonal anti-BAFF (B-cell activating factor) antibody, have not been encouraging thus far in RA patients (http://clinicaltrials.gov). To increase the effect on B-cell maturation, atacicept, a recombinant fusion protein of BAFF and the APRIL (a proliferation-inducing ligand) receptor (TACI-lg) was designed. Results of a phase I clinical trial shows a depletion of peripheral B-cells as well as decrease in rheumatoid factors (RFs) and anti-citrullinated peptide antibodies (ACPA). During the three-month study, a positive clinical effect was observed in a small group of patients; however, no significant decrease of acute phase reactants was observed [13].

2.1.8. Inhibitors of osteoclastogenesis

A monoclonal antibody against receptor activator for nuclear factor κB ligand (RANKL) denosumab is an efficient inhibitor of
osteoclastogenesis that is in phase III clinical trial in patients with postmenopausal osteoporosis. Subcutaneous administration of denosumab every six months led to significant retardation of radiographic progression in patients with active RA after one year [14]. The therapy was well tolerated, yet does not exhibit a larger effect on the disease activity.

### 2.1.9. Inhibitors of chemokines and angiogenesis

On an experimental level, blocking several specific chemokines or their receptors has been successfully tested; however, early phases of clinical trials in patients with active RA have not proven a sufficient clinical effect of monoclonal antibodies against CCL-2/MCP-1 or its receptor CCR-2 [15,16]. Angiogenesis occurs in the early phase of RA and enables chemotactic migration of inflammatory cells into the synovial tissue. A monoclonal antibody against vascular endothelial growth factor (VEGF), bevacizumab (Avastin), significantly expanded therapeutic possibilities in oncology [17]. A preclinical trial recently demonstrated a prophylactic effect of a VEGF beta monoclonal antibody in a murine model of arthritis; however, there has been no significant impact on an established disease [18].

### 2.1.10. Regulators of apoptosis

In general, cells from RA synovial tissue are resistant to apoptosis, and activated synovial fibroblasts and/or other joint tissue resident cells may presumably escape the effect of the current biological therapies (Fig. 1). Over 10 years ago, a strategy for treatment of RA that induced apoptosis by binding the FAS receptor had been introduced in an in vivo model of arthritis [19]. The first monoclonal anti-FAS IgM antibody (ARG098) was subsequently developed, and is being tested as a single intraarticular application into an active knee in a phase I clinical trial in patients with RA (http://clinicaltrials.gov).

### 2.1.11. T-cell inhibitors

Clinical trials directly targeting T-cells — alemtuzumab (anti-CD52, Campath-1H), keliximab (chimeric monoclonal anti-CD4 antibody) or clenoliximab (the IgG4 version of the previous antibody) were...
accompanied by serious adverse events linked with severe CD4+ T-
lymphocytopenia and a rash, leading to discontinuation of the clinical 
trials of these agents [20]. The improved knowledge of the co-
stimulation regulatory mechanisms and good efficacy and safety 
profile in clinical trials facilitated recently abatacept approval for the 
treatment of RA [21].

2.1.12. B-cell inhibitors

Progress in manufacturing technology led to the development of 

cocrelizumab, a humanized monoclonal antibody, and ofatumumab 
(HuMax-CD20), a fully human monoclonal antibody against CD20, 

which are in phase III clinical trials [22,23]. The results of early phases 

of studies show a good effect of both agents in patients refractory to both 

methotrexate and TNF-α inhibitors. Compared to rituximab, minimum 

immunogenicity was observed. A phase I clinical trial of a fully human 

monoclonal anti-CD19 antibody (MDX-1342) is currently in progress in 

patients with active RA (http://clinicaltrials.gov). Trubion Pharmaceuticals 
developed SMIP (small modular immunopharmaceutical), which 

binds and specifically blocks the CD20 molecule (TRU-015) and induces a 

peripheral B-cell depletion (http://www.trubion.com). A phase II 

clinical trial is currently in progress (http://clinicaltrials.gov), and re-

sults should indicate potential advantages of this agent in comparison 

with other therapeutics targeting B-cells. As this molecule is smaller 

than a standard monoclonal antibody, it is thought to have better tissue 

penetration, efficacy and safety profile.

2.2. Small molecules

More than half of the new anti-inflammatory therapies in 

preclinical and clinical trials involve small molecules, the molecular 

weights of which do not exceed 1 kDa [2]. These agents are available for 

peroral administration, should be less expensive; furthermore should 

have at least the same efficacy as the current biological therapy, and a 

reduced risk of adverse events. Recently developed small molecules 

have a targeted impact on various intercellular factors or cell struc-
tures, including receptors, intracellular signaling pathways and en-

zymes participating in the pathogenesis of RA.

2.2.1. Inhibitors of intracellular signaling molecules

Binding of an extracellular factor (e.g. a cytokine or a pathogen) to 

cell-surface receptor activates cytoplasmic kinases: mitogen-

activated protein kinases (p38, ERK, JNK) or tyrosin kinases (JAK, 

Syk), which can subsequently modulate the activity of transcription 

factors, thus regulating the expression of target genes (Fig. 2). 

Perorally administered drugs that modify the regulation of complex 

intracellular signaling pathways have been tested with a variable 

clinical response.

2.2.1.1. Inhibitors of MAP kinase p38. Based on very promising 

preclinical data, a number of pharmaceutical companies have 

developed inhibitors of MAP kinase p38 that predominantly impact 

its alpha subunit. Most of the therapeutics are in phase II clinical trials; 

the therapeutic effects have not yet reached expectations. Moreover, 

the latest data has shown that pamamipod was even less effective 

than MTX in patients with active RA [24]. Based on these data, one can 

speculate that other signaling pathways are predominantly involved 

in the pathogenesis of RA.

2.2.1.2. Inhibitors of the JAK/STAT signaling pathway. Tyrosine Janus 

kinases (JAK) can be activated by interferon-γ and other cytokines 

playing a significant role in the pathogenesis of RA [25]. Pfizer developed a 

JAK3 inhibitor (CP-690,550), which has already been in a phase II 

clinical trial in patients with moderately- to severely-active RA [26]. The 

results of this study have been very encouraging so far; after 12 months 
of administration, remission was achieved in approximately one-third of 

the individuals, and a relatively good tolerance and safety profile of the 

therapy was observed. A multicentre study is currently in progress 

comparing the effect of five dosing regimens of JAK-3 inhibitor with TNF 

inhibitor (adalimumab) and DMARDs in patients with active RA (http:// 

clinicaltrials.gov).

2.2.1.3. Inhibitors of Syk kinase. Intracellular Spleen tyrosine kinase 

(Syk) has significant immunomodulatory activity, and is stimulated by 

activation of Fcγ receptors and B-cell receptors. This signaling 

pathway is upstream MAP-kinases, especially JNK, and its activation 

plays a key role in the TNF-α induced expression of proinflammatory 

cytokines and proteolytic enzymes by synovial fibroblasts [27]. Use of 

a Syk kinase inhibitor (Fostamatinib disodium) has produced very good 

results with regard to attenuation of clinical activity of RA [28]. After 

12 weeks of peroral administration of 150 mg of the agent twice a day, 

remission was observed in almost half of the individuals. Never-
theless, the prevalence of adverse events (e.g. diarrhea, increased 

blood pressure, neutropenia and elevation of liver enzymes) increased 

due to this relatively high dosage.

2.2.1.4. Inhibitors of transcription factors. The NFκB (nuclear factor 

κB), NFAT (nuclear factor for activation of T-cells) and AP-1 

(activator protein) transcription factors have been shown to play 

the most critical roles in the pathogenesis of RA. The first 

preclinical data from an experimental model of arthritis have 

shown that treatment with c-Fos/AP-1 inhibitor (T-5224) prevents 

synovitis, osteoclastogenesis, and the subsequent destruction of a 

joint [29]. Ik kinases (IkB)-2 has been shown to play a central role 
in regulating NFκB signaling and a highly selective IKK-2 inhibitor 

has been very recently introduced to inhibit the expression of 

various inflammatory mediators as well as to block joint swelling 

and bone destruction in an experimental model of arthritis [30]. 

Another approach to inhibit NFκB, permeable NBD peptide, has 

been demonstrated through blocking the regulatory activity of 

NFκB. Its intraarticular administration into a rat joint with adjuvant 

arthritis led to significant attenuation of synovitis and joint 

destruction [31].

2.2.2. Inhibitors of cytokines and chemokines

Synta Pharmaceuticals has developed a small molecule IL-12/IL-

23 inhibitor (Apilimod mesylate), which, based on clinical results, is 

presumed to have an impact on immune response showing decrease 

of several proinflammatory cytokines and a retardation of RA pro-

gression. This drug has been successfully tested in patients 

with Crohn’s disease, and a phase II clinical trial in patients with RA 
is currently in progress [32]. A selective antagonist of a chemokine 

receptor CCR5, maraviroc, was well tolerated, without severe adverse 

events; however, due to lack of efficacy, the phase II clinical trial in 

patients with RA was terminated at the end of 2008.

2.2.3. Inhibitors of cell surface markers

RhuDex, a small molecule blocking the CD80 marker on antigen 

presenting cells, is one of the first modulators of T-cell costimulation 
available in peroral administration. A phase I clinical trial was already 
in progress, and 80 patients have been enrolled in this study so far; 

however, it was discontinued in July 2008 due to death of one vol-
unteer from myocardial infarction. The pharmaceutical company was 

requested to complete in vitro tests to exclude possible drug inter-

actions supporting atherogenesis [http://www.medigene.com].

3. Conclusions

A growing knowledge of the pathogenesis of an autoimmune 
inflammatory process has expanded the spectrum of new molecules 

and some of these may become the therapeutic targets of RA [33]. The 

therapeutic possibilities have been expanded by new monoclonal 

antibodies against several proinflammatory cytokines, chemokines,
growth factors, cytokine and chemokine receptors, or agents targeting cell surface markers. Most encouraging therapeutic strategies of recent years are small molecules; mostly inhibitors of intracellular signaling pathways. These have the advantage of peroral administration. Since intracellular signaling pathways have pleiotropic effects, focusing on the efficacy and especially the long-term safety in further studies will be needed.

There are many other targets with potential therapeutic utility approaching for example regulatory T cells (Treg) [34], Toll like receptors [35], complement pathway mediated by C5a [36] or adipokines — e.g. visfatin/PBEF [37]. The future of biological therapy may also develop according to new scientific advancements in genetic engineering, possibilities of affecting gene transcription using RNA interference with small interfering RNA or microRNA as well as possibilities of epigenetic alterations (DNA methylation and histone modifications), which may affect the regulation of inflammation and autoimmune process during the course of rheumatic disorders [38,39]. In this regard it needs to be stressed that no therapy has been targeting so far the epigenetically activated synovial fibroblasts operating the cytokine independent pathway of RA [39,40].

**Take-home messages**

- Spectrum of monoclonal antibodies are currently tested in clinical trials including TNF-α inhibitors (golimumab, certolizumab pegol), inhibitors of several pro-inflammatory cytokines such as IL-1, IL-6, IL-12, IL-15, IL-17, or IL-23, and agents targeting B-cells (ocrelizumab, ofatumumab, TRU-015).
- Small molecule inhibitors, particularly inhibitors of JAK3 and Syk kinases, are currently the most encouraging therapies for rheumatoid arthritis; however long-term efficacy and treatment safety have yet to be shown.
- Treg cells, innate immune system, several new cytokine-like molecules, RNA interference or epigenetic alterations expand the spectrum of new promising targets for autoimmune disorders.

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*Fig. 2.* Schematic drawing of signal transduction pathways and transcription factors, and their potential modulation by peroral inhibitors. Upon exposure of a cell to stress, proinflammatory environment, cytokines or pathogens, several regulatory enzymes are phosphorylated and activated. As a result, an intracellular signaling cascade is activated to transmit the signal from a receptor via MAP and tyrosine kinases to transcription factors, which affect the expression of genes for cytokines, matrix metalloproteinases, apoptosis regulating molecules, proliferation, etc. Inhibitors of Syk kinase and Jak3 have been most successful in clinical trials in patients with rheumatoid arthritis so far. MAPK, mitogen-activated protein kinase; MAPKK, MAPK kinase; MAPKKK, MAPKK kinase; Jak, Janus tyrosine kinase; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase; IκB, inhibitor IκB; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinases; NF-κB, nuclear factor-κB; AP1, activator protein 1; ATF2, activating transcription factor 2, TNF, tumor necrosis factor; IL, interleukin; MMPs, matrix metalloproteinases.
Acknowledgments

The study was supported by Ministry of Health of Czech Republic, research project no. 00023728.

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(Continued...)

Treatment of myositis-associated lung disease with intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been used to treat severe and refractory autoimmune conditions. In a recent description, Suzuki et al. (Lung 2009;187:201-6) have retrospectively evaluated the safety and efficacy of IVIg in five patients with acute refractory myositis-associate lung disease myositis patients (one polymyositis and 4 amyopathic dermatomyositis). The authors described that three of these subjects died of an acute respiratory failure within a three months period and two survived. They did not observe any differences regarding clinical characteristics and course of the disease among those that survived and those who did not. The authors concluded that given the very poor prognosis of myositis-associated lung disease patients, IVIg use can be safe and effective for a subgroup of these individuals.