A glimpse into the future: recombinant proteins and small molecules for targeted therapies in rheumatic diseases

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ABSTRACT

Whether the differences in the clinical picture and in the pathogenesis between rheumatoid arthritis (RA) and ankylosing spondylitis (AS) will lead to different therapeutic approaches is unclear at present. Since anti-TNF-α agents and other biologics are not efficacious in all patients new developments are clearly needed.

Introduction

Among the intercellular communicating molecules cytokines such as IL-12, IL-17 and IL-23 are promising new targets. Signalling overlap between various cytokines such as RANKL, TNF-α and IL-1, converges at the NF-kappaB and MAPK signal transduction pathways. The alternative to inhibition of extracellular cytokine effects on intracellular cytokine transcription is the therapeutic modulation of intracellular signalling systems, that provide the link between the receptor signalling and nuclear gene transcription, one example of likely importance in RA the p38 mitogen-activated protein kinase pathway. Spleen tyrosine kinase (syk) is a key regulator in the signal pathway of mast cells and in the regulation of IgG and IgG Fc receptor expression, the inhibition of syk seems to be associated with clinical improvement in RA. The introduction of TNF blocking biologic therapies has revolutionized treatment options for rheumatic diseases, specifically for rheumatoid arthritis (RA) and ankylosing spondylitis (AS). However, there are some shortcomings of this novel therapy including the lack of efficacy in quite a significant proportion of patients, loss of efficacy over time, risk of infections and high costs, which have initiated enormous efforts to identify novel potential targets. These targets include intercellular communication pathways, as members of the pro-inflammatory cytokine network, cell surface receptors systems and intracellular signalling pathways such as protein kinases. Although this research area is growing rapidly, only a few small molecules or recombinant proteins have made their progress to being used in clinical trials. These new treatment principles are specifically explored in RA.

Intercellular targets

Among the intercellular communicating molecules, cytokines remain highly promising targets. Specifically IL-17 has been shown, at least in animal models, to be involved in both, osteoclastogenesis and osteoblastogenesis (1). Because of its role in synovial inflammation, cartilage and bone destruction (1, 2) and possibly in new bone formation (3) IL-17 seems to be a promising target for both, RA and AS. Clinical trials are on their way, results, however, are not yet available.

IL-15 is a cytokine with multiple functions within the immune system. There are clear data indicating a central role of IL-15 in the pathogenesis of RA by inducing TNF-α and IL-17. IL-15 receptor α chain and a mutant IL-15/Fcγ 2a fusion protein prevented the development of arthritis and reduced the severity of disease in animal models (4, 5). Based on these results, a recent open-label clinical trial yielded ACR 20, 50 and 70 response rates of 63, 38 and 25% of the treated RA patients (6).

RANK ligand, an initiator of osteoclast development and activation, has also been targeted in several rodent arthritis models applying osteoprotegerin (7, 8). Human trials are thus far limited to the application of OPG-Fc (9) and the anti-RANK antibody denosumab (10) in post-menopausal women.

Available data point to a considerable signalling overlap between various cytokines such as RANKL, TNF-α and IL-1, which converges at the NF-kappaB

and MAPK signal transduction pathways. Notably, ligation of RANKL, TNF or IL-1 to their respective receptors induces recruitment of adapter proteins, and kinases that direct the signalling cascades towards relevant inflammatory and osteoclastogenic transcriptional regulations (11, 12).

Intracellular targets

An alternative to the inhibition of extracellular cytokine effects on intracellular cytokine transcription is the therapeutic modulation of intracellular signalling systems that provide the link between the receptor signalling and nuclear gene transcription. The p38 mitogen-activated protein kinase pathway seems to be of specific importance in RA (13). Blocking the p38 MAP kinase by small molecules ameliorated experimentally induced arthritis (14, 15). However, in a recent placebo-controlled, double-blind study, evaluating the efficacy, pharmacodynamics and safety of a novel p38 MAP kinase inhibitor in RA patients, only a modest clinical efficacy including a transient suppression of biomarkers of inflammation was reported. This study suggests that p38 MAP inhibition might not provide clinically meaningful and sustained suppression of chronic inflammation in RA (16).

Other interesting targets are the Janus-kinase signal transducer and activator of transcription (Jak/STAT) and suppressors of cytokine stimulation (SOCS) (17-19). However, data from clinical trials in human autoimmune rheumatic diseases are still missing.

More recently, it was demonstrated that the inhibition of c-kit tyrosine kinase by imatinib mesylate might be effective in treating RA patients, specifically in situations where patients are refractory to other treatment principles (20, 21). However, larger and placebo-controlled studies are necessary to identify a possible role for imatinib mesylate in the treatment of autoimmune rheumatic diseases.

Of special interest are recently published data indicating that the spleen tyrosine kinase (Syk) could serve as a novel and promising target for immune intervention in rheumatic diseases. Syk is a key regulator in the signal pathway of mast cells and in the regulation of IgG and IgG Fc receptor expression. Syk has also a central role in the signalling pathway leading to osteoclastogenesis. The small molecule R88 was recently demonstrated to ameliorate established disease in NZB/WF1 mice as well as in MLR/lpr mice and was also shown to reduce significantly clinical arthritis in a CIA arthritis model. In a recently performed randomized, double-blind, placebo-controlled study, the preliminary efficacy of R7A8 in RA patients was evaluated over a trial period of 12 weeks. With regard to the efficacy a reasonable high percentage of patients achieved ACR 20, 50 and 70 applying doses of 50, 100 or 150 mg BID for 12 weeks. The authors state that the responses were similar to reported responses with TNF inhibitors. Safety and tolerability was acceptable. Until now, approximately 220 patients have been treated in phase II trials in RA and in lymphoma patients and ITP patients. At present a placebo-controlled, double-blind, multi-center study is presently performed to assess the efficacy of blocking spleen tyrosine kinase in RA patients (22).

Searching the literature for clinical trials applying small molecules for the treatment of patients with different rheumatic diseases, until now only a few molecules have been successfully tested regarding clinical response rates in such trials. However, with further information on the molecular biology of intracellular signalling pathways, more small compounds will be developed, which might turn out to show clinical efficacy and safety profiles similar to TNF-α blockers.

All these agents have not been studied in spondyloarthritides as yet.

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