F1000 MEDICINE REPORTS

Published: 14 September 2009

Clinically relevant advances in rheumatoid arthritis therapy

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F1000 Medicine Reports 2009, **1**:68 (doi:10.3410/M1-68)

Abstract

Owing to the success of biologics in the treatment of rheumatoid arthritis (RA), several novel drugs have been introduced in the therapeutic armamentarium, although not all of them have been approved in all countries worldwide. Among the drugs are tumour necrosis factor (TNF) inhibitors such as certolizumab pegol and golimumab (the latter of which was the first TNF blocker shown to be effective in patients who had been unsuccessfully treated with other TNF blockers and which can be applied only once a month), and the interleukin-6 receptor antagonist tocilizumab, which not only opens up a completely new field of anti-inflammatory modulation of RA pathophysiology, but also highlights the challenge of novel potential side effects. Moreover, aside from clinical studies showing efficacy in the inhibition of osteoclast activation by the anti-RANKL (receptor activator of nuclear factor-kappa B ligand) antibody denosumab, an improved form of steroid application known as slow-release 'tempus tablet' for treatment of RA and several developments in the small-molecule area have been addressed by clinical trials.

Introduction and context

The pathophysiology of rheumatoid arthritis (RA) provides numerous cellular, intracellular, and messenger molecule targets, which can all be addressed by biochemical as well as antibody-based biological therapeutic agents. On the other hand, none of the current therapeutic regimens for RA leads to a long-term 100% remission rate, so additional ideas and drugs still need to be continuously developed and tested in clinical trials. These developments also include improvement of current drugs in terms of safety, efficacy, and a more comfortable application for the individual patient. Here, some of the most important developments in this field are presented.

Recent advances

Improvements in and around the gold standards

A milestone in the development of the therapeutic armamentarium for RA is the modified application form of prednisolone, which consists of prednisolone embedded in an inert hull that disintegrates after 3-5 hours of intestinal transit time and releases the prednisolone precisely at the moment of the lowest endogenous steroid production in the early morning hours. When this 'tempus tablet' (Figure 1) was applied, significantly reduced morning stiffness could be achieved [1]. Similarly, as shown in a recent study, the disease-modifying anti-rheumatic drug (DMARD) gold standard, methotrexate, is significantly more effective when applied subcutaneously and provides a more rapid onset of the therapeutic effect [2]. Another strategy in the small-molecule DMARD field is the mitogen-activated protein (MAP) kinase inhibitor pamapimod. Although MAP kinases are ubiquitous in inflammatory cells and contribute significantly to the synovial activation, the primary goal of an efficacy that was better than that of methotrexate could not be achieved [3,4]. As shown recently, targeting other intracellular kinases such as Jak and Syk might be more promising. The most recently published study, in which masitinib (a potent and selective protein tyrosine kinase inhibitor of c-kit) was tested in the monotherapy treatment of DMARD-refractory RA, showed ACR20/50/70 (American College of Rheumatology 20%/50%/70% improvement criteria) scores of 54%, 26% and 8%, respectively, and a

Figure 1. 'Tempus tablet' for the delayed release of prednisolone when taken orally at bedtime (10 p.m.)

The hull of the tablet breaks apart after 4-6 hours of intestinal transit time, and prednisolone can act immediately at the time of the lowest endogenous steroid production. Photograph taken by UM-L.

reduction in C-reactive protein level by greater than 50% for approximately half of the patients [5].

Next generation tumour necrosis factor inhibitors

Approximately 10 years after the introduction of the first tumour necrosis factor (TNF) inhibitor (infliximab), there is still room for development and improvement (for example, a more rapid response or achievement of remission, or both, and an improvement of application mode for the patient). The first biologic in this group is the pegylated TNF inhibitor certolizumab pegol (CEZ), which has shown a very rapid response in clinical trials [6,7]; it has been hypothesized that the pegylation may also lead to a deeper penetrance of the drug into the joints, an idea that still needs to be proven. It is licensed for RA in the US and has just received a positive appraisal from the European Medicines Agency and is approved for Crohn's disease in some other countries (such as Switzerland). However, the overall response rates do not differ significantly from those of the other TNF inhibitors. The second novel TNF inhibitor, golimumab (GOM), is – aside from adalimumab – the second fully human TNF inhibitor and was developed with the goal of achieving a once-a-month patient-friendly subcutaneous application [8,9]. As this goal has been achieved in clinical trials with an efficacy comparable to those of the other TNF inhibitors, GOM was also recently licensed for RA in the US and is expected to be launched in Europe late this year.

Additional novel targeted therapies

To improve the earlier approach of a biologic inhibition of the proinflammatory and chondrocyte-activating molecule interleukin-1 (IL-1), ACZ885, a fully human monoclonal antibody that neutralizes the bioactivity of human IL-1β, was generated in a small proof-of-concept study of 32 patients [10]. A statistically significant reduction in disease activity score was observed after 4 weeks in the 10 mg/kg group, with a rapid onset of action in responders within the first 3 weeks. However, the true value of IL-1 inhibition, which is significant in fever syndromes and adult Still's syndrome, remains to be proven for long-term RA. With regard to the idea of selectively reducing the activity of the bone-degrading osteoclasts by antagonizing RANKL (receptor activator of nuclear factor-kappa B ligand), the addition of twice-yearly injections of denosumab to ongoing methotrexate treatment inhibited structural damage for up to 12 months in patients with RA, with no increase in the rates of adverse events as compared with placebo [11,12].

The more prominent development, however, was the licensing of the humanized anti-IL-6 receptor antagonist tocilizumab (TOZ) for RA in some countries in Europe. (Note: In this report, the abbreviations CEZ, GOM and TOZ are used according to a proposed unifying system for the nomenclature of biologics [13]). On the basis of the results of the clinical trials, TOZ, unlike other biologics, has been approved both for monotherapy and for first-line biological treatment similar to first-line TNF inhibitors. The data of the clinical studies [14,15] show a rapid and persisting effect, which is further supported by the interesting notion that, due to the very early approval in Japan for Castleman's disease, 5-year efficacy and safety data are already available. However, although in Europe several hundred patients have already been treated in the clinical routine, novel side effects also have to be considered in daily practice. First, it needs to be noted that, similar to TNF, IL-6 is a pluripotent cytokine with numerous (differing) effects in pathways modulating inflammation and growth, but with fewer effects in the TNF domains of atypical and opportunistic infections and the development of lymphoma. Second, the side effects of IL-6 inhibition are important in many other clinically relevant settings [for example, (transient) leukopenia and thrombopenia, the elevation of serum lipids, and hitherto unexplained gastrointestinal perforations].

Implications for clinical practice

Therapy of RA is still a challenge for the practising rheumatologist, not only because none of the current drugs or combination therapies is able to achieve long-term full remission but also because the majority of

patients are currently experiencing a loss of efficacy of the first, second, or even third biologic, so that novel options are urgently needed. The recent developments in the field of TNF inhibitors and the novel IL-6 inhibitor TOZ are potentially an option for these needs. Moreover, the developments in the small-molecule field may be able to provide an applicable drug in the near future, although sustainable efficacy and clinically acceptable side effects still need to be proven in large-scale clinical trials. On the other hand, the novel application form of prednisolone, which has been manufactured according to the circadian need for an in-time delivery of steroids in the early morning hours, may contribute significantly to decrease the steroid load for RA patients. In summary, treatment of RA has become more colourful but also more challenging.

Abbreviations

CEZ, certolizumab pegol; DMARD, disease-modifying anti-rheumatic drug; GOM, golimumab; IL, interleukin; MAP, mitogen-activated protein; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-kappa B ligand; TNF, tumour necrosis factor; TOZ, tocilizumab.

Competing interests

With respect to products mentioned in this report, UM-L has received speaker honoraria from Abbott (Wiesbaden, Germany), Amgen (Munich, Germany), Chugai Pharma (Frankfurt, Germany), Essex Pharma (Munich, Germany), Merck Sharp and Dohme (Munich, Germany) and UCB (Monheim, Germany); IHT has received speaker honoraria from Abbott; and EN has received speaker honoraria from UCB.

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