Targeted therapies in rheumatoid arthritis
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CHAPTER 1

General introduction
RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic disease characterized by inflammation of the synovial tissue and destruction of the adjacent cartilage and bone. The clinical presentation usually exists of a symmetric polyarthritis of the small joints of hand and feet, but any joint can be involved. Patients present with tenderness, swelling and impaired movement of their joints. Extra-articular manifestations can also be observed, such as subcutaneous or pulmonary nodules, pleuritis, pericarditis, vasculitis and interstitial pneumonitis. RA affects 1% of the population and is associated with increased morbidity and mortality. RA is considered an autoimmune disease, in part because of the presence of auto-antibodies, such as IgM-rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), of which especially ACPA are highly specific for RA and thus can be used as a diagnostic tool. Auto-antibodies can be found already before the start of clinical manifestations, and their presence in 70-80% of the patients is associated with a more severe and destructive disease phenotype. Until last year, the 1987 ACR criteria were used as classification criteria for the diagnosis of RA. Patients should fulfil four out of seven of the following criteria: morning stiffness of at least one hour, arthritis of ≥ 3 joint areas, arthritis of hand joints, symmetric arthritis, subcutaneous nodules, presence of RF and presence of erosions. Because of a great improvement in the management of RA over the last decade and because it has been recognized that early therapeutic intervention improves clinical outcomes, the 1987 criteria, which are meant for classifying established RA, have been replaced by the ACR/EULAR 2010 criteria. The 2010 criteria have been developed to identify patients who would benefit from early therapeutic intervention, thereby preventing the development of late stage, erosive and nodular disease.

PATHOGENESIS

Although the exact pathogenesis is not known, an interplay of several genetic, environmental and stochastic factors together contribute to the development of RA. Findings in twin studies estimated the relative contribution of genes to be around 50%, of which the disease association with HLA-DR4 alleles (which contain the shared epitope) is best established. The best established environmental factor is cigarette smoking, especially in HLA-DR4 positive individuals. Given that smoking promotes citrullination of self proteins, it might be directly linked to formation of ACPA. Data from genetic epidemiological studies show that the three risk factors HLA-DR allele positivity, smoking and presence of ACPA in the serum all contribute independently to a higher risk of development of RA. In addition, recent findings support the hypothesis that periodontitis, the most common oral disease, is an etiological factor for RA as well. Normally, the synovial membrane is a relatively acellular and avascular structure with an intimal lining layer consisting of one or two cell layers. In RA, macrophages, T cells, B cells and plasma cells infiltrate the synovium and sometimes organize into lymphoid aggregates. In addition to ingress of leukocytes, hyperplasia of the resident fibroblast-like synoviocytes occurs, contributing to an increased cell mass, called pannus, which behaves like a locally growing tumor invading adjacent articular structures, eventually resulting in bone erosions. Furthermore, the
hypoxic environment in the synovial tissue promotes abundant neo-vascularisation, resulting in even more cell ingress, thereby creating a positive feed-back loop.\textsuperscript{17}

Interestingly, there are two fundamentally different viewpoints on the pathogenesis of RA, dealing with the chicken or the egg causality dilemma. Arthritis may start primarily in the synovial membrane, subsequently spreading and penetrating into the bone marrow. This notion is supported by studies suggesting that the inflamed synovium has highly invasive potential. Alternatively, arthritis may start in the bone marrow and then migrate to the lining of the joint; this view is supported by the observation of MRI-based osteitis and lymphocytic infiltrates in bone marrow fat found in the early stage of disease (reviewed in \textsuperscript{18}). Conceivably, both mechanisms are important.

HETEROGENIC DISEASE: NEED FOR BIOMARKERS

It is becoming more and more accepted that the phenotype described as RA is a clinical syndrome consisting of several pathogenetically different disease subsets instead of one disease.\textsuperscript{19} This has become evident based on the heterogeneity of the clinical picture, the difference between autoantibody positive versus autoantibody negative disease, the presence of erosive disease and self-limiting versus persistent disease, but also by the differential response to different targeted therapies.\textsuperscript{20} In addition, patients can be divided into two subsets based on the expression of a type I interferon signature in the peripheral blood cells; in some patients this expression is similar, whereas in others it is elevated compared to the levels found in healthy individuals.\textsuperscript{21}

At present, the heterogeneity of the disease and the lack of definitive clinical features and biomarkers may result in a delay in diagnosis and subsequently a delay in initiation of patient-specific treatment. Furthermore, since the choice of targeted therapies for RA is growing and only a subset of patients respond to each therapy, there is a strong need for biomarkers that can predict clinical response to different therapies.

CURRENT TREATMENT REGIMEN

From the introduction of disease-modifying anti-rheumatic drugs (DMARDs) several decades ago, the therapeutic range of treatments for RA underwent dramatic developments. The first important shift in treatment approach was the wider use of methotrexate which replaced intramuscular gold therapy as the first-line DMARD.\textsuperscript{22,23} The combination of good efficacy and acceptable toxicity in many patients as well as low costs explains why methotrexate treatment is still (part of) the first treatment step. The second important shift was the introduction of targeted therapies, consisting of monoclonal antibodies or receptor constructs, created by bioengineering, called biologicals, as well as very recently targeted small molecules. When the treatment goal is not reached with methotrexate alone, it can be combined with other DMARDs (sulphasalasine, leflunomide, hydroxychloroquine or gold) or with a biological.\textsuperscript{24} Addition of low-dose glucocorticoids is usually also very effective, but since its side effects it is preferentially used temporary for bridging between two therapies. TNF\textsuperscript{\alpha} blocking therapy was the first category of biologicals that turned out to be very successful.\textsuperscript{25-27} At present there are five different TNF blockers on the market: infliximab, adalimumab, etanercept, golimumab and
certolizumab pegol, of which the last two were recently registered. According to the current treatment algorithm, if TNF-blockade is not effective, the next step is to switch to another TNF-blocking agent or to switch to one of three other registered biologicals: rituximab, abatacept or tocilizumab.\(^{19,24}\) Rituximab is a CD20-directed B cell depleting antibody, which will be extensively introduced in chapter 2 and 3 of this thesis. Abatacept is a fusion protein, consisting of the extracellular domain of human CTLA-4 connected to the Fc-tail of human IgG1, which outcompetes the binding of CD28 on a T cell with CD80 and CD86; its exact working mechanism is as yet unknown.\(^{28}\) The humanised antibody tocilizumab is directed against the interleukin-6 receptor.\(^{29}\) Together, they form the main pillars of the current targeted therapy.

Interestingly, all of the currently registered biologicals show on the group level similar clinical responses: ACR20 responses of around 70% in methotrexate inadequate responders and around 50% in anti-TNF inadequate responders, so a considerable proportion of patients does not respond satisfactorily to each biological. A minority of patients reaches complete remission of the disease and a small subset of patients does not respond to any of the available treatments. In addition, the clinical response can diminish over time due to formation of anti-drug antibodies. Thus, there is still a clear unmet need in the treatment of RA. Future therapeutic strategies will include concepts of personalized medicine as well as the use of new mechanisms of action.\(^{19,24,30}\)

Taken together, although there have been major breakthroughs during the last years, long-lasting remission is achieved in only a minority of the RA patients all, so current treatment regimens need to be optimised and new therapeutic targets should be studied.

FROM BENCH TO BEDSIDE...

Because of the increasing knowledge about the pathogenesis of RA, new potential targets are identified and novel compounds are designed hoping for the desired effect on the target. After in vitro efficacy and/or after an effect in animal models of arthritis has been shown, the compound can be tested in humans with appropriate preclinical toxicology studies in place. Clinical trials involving new drugs are commonly classified into four phases. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through phase I (first in human), phase II (dose finding and initial efficacy), and phase III (efficacy in large patient groups), it may be approved by the national regulatory authority for use in the general population. Alternatively, before the start of a large conventional clinical trial, the initial efficacy can be tested in a compact high density-of-data clinical trial design with serial mini-arthroscopies to obtain synovial tissue before and after treatment.\(^{31}\) We have previously proposed that three checkpoints should be considered before a decision towards full drug development is made in terms of a ‘go’ or a ‘no-go’ decision: (trend towards a) clinical improvement, a specific biological effect related to the mechanism of action and a change in synovial sublining macrophage numbers, which has been proven to be a sensitive biomarker of clinical response in RA patients.\(^{32}\) This design allows selection during early drug development in a relatively small number of patients. If there is a positive signal in at least one of these three criteria, the recommendation would be to test whether this translates into clinically meaningful effects in phase III trials on larger patient groups.\(^{31}\) Phase IV trials involve the safety surveillance and ongoing technical support of a drug after registration.
AND FROM BEDSIDE BACK TO BENCH

After a successful targeted therapy has been approved and is broadly used in the clinic, its specific mechanism of action may still be in part unknown. Systematic studies of biosamples from RA patients obtained from before and after initiation of a targeted therapy may be informative to provide a deeper understanding of the specific mechanism of action and may result in more insight into the pathogenesis of RA. After all, the more we know about a disease, the better we may be able to treat it.

OUTLINE OF THIS THESIS

This thesis contains studies aimed at improving our knowledge about the pathogenesis of RA and revealing why therapies are effective or not effective in subsets of patients, with the final goal to optimize the treatment of RA patients. It is divided into two sections:

Section I discusses both the mechanism of action and the clinical use of rituximab. Chapter 2 and chapter 3 summarise what is already known about the mechanism of action of rituximab in RA and describes possible mechanisms of how B cell depletion could result in a clinical response. Rituximab is not only effective in reducing clinical activity, but it also inhibits the progression of joint destruction by as yet unknown mechanisms. Osteoclasts are cells of the bone specialised in bone destruction and promote the development of erosions. In chapter 4 we study the effect of rituximab on osteoclastogenesis in RA patients.

Currently, the dosing schedule of rituximab consists of 2 infusions of 1000 mg with an interval of 14 days. Since dose-finding studies for the use of rituximab in RA are limited, we are not sure if this is the optimal dosing schedule. Chapter 5 evaluates if rituximab serum levels are related to progression of joint destruction, to explore the question if a higher dose could result in further inhibition of progressive joint destruction. In contrast, data from a recent study suggested that after induction of clinical response with 2x1000 mg rituximab, re-treatment with rituximab might be possible in a lower dose. We explored this in 9 RA patients in chapter 6.

Since the choice of targeted therapies for RA is growing and only a subset of patients respond to each therapy, there is a strong need for biomarkers that could predict clinical response to different therapies. In chapter 7 we tested if the presence of a type I interferon signature in the peripheral blood of RA patients is associated with non-response to rituximab and thereby could be used as a biomarker for response.

Section II describes two phase I/IIA clinical trials with new compounds for the treatment of RA. In chapter 8 the monoclonal antibody ASK8007, which blocks osteopontin, was tested in a randomised, placebo-controlled proof-of-concept study. Chapter 9 describes a phase IIA trial in which the safety, tolerability and initial efficacy was tested of apilimod mesylate, an oral small-molecule compound that could inhibit the production of IL-12 and IL-23.

A summary and general discussion is provided in chapter 10. Herein, future plans are proposed to further improve the treatment of RA patients.


