Targeted therapies in rheumatoid arthritis
Boumans, M.J.H.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Download date: 22 Jan 2019
CHAPTER 10

Summary and general discussion
This thesis describes studies aimed at improving the current treatment of rheumatoid arthritis (RA) patients. Specifically, we studied how to improve the current treatment regimen of rituximab and we tested inhibitors of two new potential targets, osteopontin and interleukin-12 and-23, for the treatment of RA.

BACKGROUND

RA is a chronic autoimmune disease leading to inflammation of the synovium. RA is found in about 1% of the population, more often in women than in men. Typically, a patient presents with pain, morning stiffness and swelling of the small joints of hands and feet, but other joints and other organs may be affected as well. The inflammatory response is often accompanied by joint destruction with loss of cartilage and formation of erosions in the underlying bone.

The diagnosis is primarily made based on the clinical presentation. Autoantibodies are found in about 70% of the patients. In particular, antibodies directed to citrullinated proteins have high specificity for RA and their presence is often associated with a more severe and destructive course of the disease.1

The cause of RA is not entirely clear. Probably a combination of factors is involved. There are for example several genes known to increase the risk of developing RA and smoking appears to play a major role. Recent findings also suggest a relationship between the onset of RA and the presence of periodontitis, or inflammation of the gums and bone around the teeth, partly because the bacteria that causes periodontal disease makes an enzyme that is able to citrullinate proteins.2;3

In recent years, the treatment of RA has greatly improved, in part because of the introduction of the so-called ‘targeted therapies’.4 They are specifically directed against a single target within the dense network of inflammatory cells and mediators driving RA, which may ultimately reduce inflammation in its entirety. There are four main pillars on which the current targeted treatment is based: anti-TNF alpha therapy, anti-B cell therapy, modulation of costimulation by abatacept and anti-interleukin-6 receptor therapy.5

Despite great progress, still many unresolved issues exist in the treatment of RA. For example, a small proportion of the RA patients does not respond to any treatment or loses response over time. It is also not sufficiently clear whether subgroups of patients can better be treated with one drug, while others are better off with another drug. Currently, the choice for a specific therapy is largely a matter of trial and error. This is disadvantageous for several reasons: patients are sometimes unnecessarily exposed to side effects, it is expensive and it is time consuming, since it often takes at least 3 months to evaluate the clinical response. It would therefore be very useful if we could find biomarkers predictive of the response to treatment, to facilitate ‘personalized medicine’.

Together with the need to improve individualized treatment strategies, there is still a requirement to develop new treatments. Mechanistic studies in RA patients may help to identify such therapeutic targets. In addition, they may provide insight into the specific mechanism of action of how a ‘targeted therapy’ leads to a clinical effect. Studies of the molecular events at the site of inflammation following targeted treatment may also reveal important aspects of the pathogenesis of RA. Mechanistic studies could also help in finding appropriate alternative treatments for patients not responding to a specific therapy.
MAIN FINDINGS

Section I. The mechanism of action and clinical use of rituximab. Rituximab is an antibody directed against the CD20 molecule on B cells, leading to B cell depletion. In chapter 2 and 3, we summarize what is known about the effects of rituximab on the different compartments of the immune system and the differences in these effects between patients with and without a clinical response. The difference in response could be explained by a difference in B cell depletion. Both in the bone marrow and in the synovium, there is variable depletion of B cells, whereas nearly all B cells are depleted in the blood after rituximab treatment.6-14 There are several possible reasons that could explain this variability. Firstly, individual differences may exist in the expression of survival factors for B cells. A polymorphism of B Lymphocyte Stimulator has for instance been associated with the response to rituximab.15 Second, the effector mechanisms by which rituximab depletes B cells may differ between patients. In lymphoma patients, it is known that differences in essential factors for antibody- or complement-dependent cytotoxicity can explain heterogeneity in the clinical response 16, but for RA these studies are lacking. Non-responders could also have B cells that are less sensitive to rituximab. For instance, several studies have shown that memory B cells are more resistant to the effects of rituximab than naive B cells, by an as yet unknown mechanism.8-10 Besides a difference in B cell depletion, the indirect effects of B cell depletion on other cell populations may differ between patients. Accordingly, we have shown that the decrease in synovial plasma cells differs between responders compared to non-responders to rituximab.17

From the large phase III trials it is known that rituximab is not only effective in reducing clinical activity of RA, but that it also inhibits progressive joint destruction, even in patients who show no clinical effect. In chapter 4 we studied the mechanism by which rituximab diminishes the progression of joint destruction. We found that 16 weeks after rituximab treatment RANK-positive osteoclast precursors almost completely disappeared from the synovium, and that both in the blood and the synovial tissue the osteoclast-stimulating factor RANKL decreased more than the decoy receptor for RANKL, OPG. This could explain the inhibition of bone destruction by rituximab. The dynamics in the OPG/RANK/RANKL system after rituximab treatment can probably be explained by a combination of direct and indirect effects of B cell depletion; a recent study showed that synovial B cells can express RANKL themselves as well.18 In addition, it was recently shown in mice that a specific type of B cells normally residing in the peritoneal cavity, B1-cells, has the ability to differentiate into osteoclasts.19 An example of an indirect effect is that B cell depletion leads to a decrease of synovial T cells, which are important producers of RANKL. Taken together, these data show a link between inflammation and formation of erosions in RA patients. The theory that two different pathological processes exist; one resulting in synovitis and the other resulting in osteitis and eventual formation of erosions, could still be correct 20, but then B cells must participate in both processes.

It is currently unknown whether the registered dose of rituximab is high enough to reach maximal efficacy in RA patients. The use of rituximab for the treatment of RA has been adapted from the oncology field, where it is used for the treatment of B-cell lymphomas. In previous studies only two different doses were tested for RA patients. Recently, the IMAGE trial showed that in the first 6 months patients treated with the higher dose of rituximab (2x1000 mg) exhibited a better inhibition of joint destruction, whereas the higher and lower doses induced a comparable clinical response21, suggesting that rituximab may have a different dosage effect for
inhibition of joint destruction compared to the effect on disease activity. Therefore, we studied in chapter 5 whether the degree of inhibition of progressive joint destruction is dependent on the serum rituximab levels. We found that this was not the case, suggesting that an even higher dose of rituximab would not result in stronger protection against joint destruction. On the contrary, the IMAGE trial also showed that after 6 months there is apparently no difference between the two doses both in terms of clinical efficacy and of inhibition of destruction. Based on these findings, we explored a different treatment regimen: induction therapy with 2 x 1000 mg rituximab followed by retreatment with 2 x 500 mg (or 1 x 1000 mg as this would be more convenient to the patient) after 6 months. In chapter 6, we showed in 9 RA patients that both the clinical response and the inhibition of structural damage induced by 2 x 1000 mg rituximab might be sustained in most RA patients by retreatment with 1 x 1000 mg rituximab rather than with the current retreatment regimen of 2 x 1000 mg. This treatment regimen is cost-effective, patient friendly and might perhaps have an advantage in terms of safety as well, but this needs to be shown in markedly larger studies in the future, for which this study provides the rationale.

Previous work has shown that the mononuclear cells in the peripheral blood of a subset of RA patients show activation of type I interferons (IFNs) (type I IFN signature) compared with cells from healthy controls. Interestingly, type I IFNs can have a role in the survival of B cells and therefore the presence of a type I IFN signature could be related to non-response to rituximab. In chapter 7, we found that patients with a type I IFN signature responded less well to rituximab on the group level. Future research is needed to address the question if this signature, possibly in combination with other clinical and molecular biomarkers, can also be used to predict the response at the individual level in the context of personalized health care.

Section II. Evaluation of potentially new treatments for rheumatoid arthritis. In chapter 8 and 9, we studied two new drugs for the treatment of RA. ASK8007 is an antibody directed against osteopontin, a pleitropic protein with several functions in the immune system, such as the recruitment of inflammatory cells and the adhesion of osteoclasts to the bone matrix. In vitro studies and studies in animal models of RA showed promising results with this antibody. We studied ASK8007-treatment for the first time in a randomized, placebo-controlled clinical trial that is described in chapter 8. The drug was well tolerated and was detectable in the synovial fluid, indicating that it reached the site of inflammation. However, compared to the placebo-treated group, no effect was found on the primary endpoints of the study: not on measures of disease activity nor on synovial biomarkers. Hence, we concluded that ASK8007 is not an effective treatment for RA and our data do not support further drug development for ASK8007.

Finally, in chapter 9, the drug apilimod was tested in RA patients with a similar placebo-controlled study design. Apilimod selectively inhibits the production of protein-40, which is shared by interleukin-12 and -23, two mediators playing an important role in T cell biology. In this study we found no robust effect on disease activity. Apilimod was also poorly tolerated, especially in the higher dose of 2 x 100 mg where all patients experienced gastro-intestinal complains. Of note, the expression of interleukin-12 and -23 in the synovium did not decrease after apilimod treatment, implying that the drug is not inhibiting the formation of interleukin-12 and -23, in other words it is not doing what it should do in vivo. We concluded that apilimod has no place in the treatment of RA, but that interleukin-12 and -23 can as yet not be discarded as potential therapeutic targets based on the findings in our study. Currently, two other therapies
exist that also target IL-12/IL-23, the monoclonal antibodies ustekinumab and briakinumab, of which the first one has recently been approved for the treatment of plaque psoriasis, an auto-immune disease of the skin, and the second one is currently under investigation for the treatment of RA. 24

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In this thesis, we studied targeted therapies for the treatment of RA. We aimed at clarifying the mechanism of response and non-response to rituximab and tried to further improve the current treatment regimen. We found that targeting B cells results in beneficial changes of the RANK/RANKL/OPG axis, thereby proving an important role of B cells in joint destruction. Future studies should focus on the pathophysiology of the patients in whom joint destruction is not inhibited by rituximab, aiming at improvement of treatment for these patients. Based on the results of translational studies we conclude that most likely, clinical non-response is related to persistence of B lineage cells in the tissues and that suboptimal dosing of rituximab is not necessarily the explanation. Future research should tell us more about the phenotype of these persistent B cells and factors including for instance stromal cells that keep these B cells at the site of inflammation. Furthermore, other compartments of the immune system where B cells could hide should be explored, like lymph nodes. Individual differences between responders and non-responders should continue to be studied as well, to be able to predict response on the individual level in the future using combinations of different clinical and molecular biomarkers.

In addition, we tested two new targeted therapies in active RA patients. Both therapies did not induce improvement of disease activity, resulting in a no-go decision for further drug development. For osteopontin, it can be concluded that this is probably not a good target, while IL-12/IL-23-inhibition might perhaps still have a place in the treatment of RA.

Future research should continue to focus on unraveling the heterogeneity of RA, making it possible to refine personalized treatment regimens. In addition, in light of the existing unmet needs, there is room for new treatments. Together, this may help to reach the ultimate goal: remission in all RA patients.

REFERENCE LIST


