B cells and B cell directed therapies in rheumatoid arthritis: towards personalized medicine
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GENERAL DISCUSSION

INTRODUCTION
Within the past decade a number of novel effective treatments have become available for rheumatoid arthritis (RA), among which tumor necrosis factor (TNF) blockers, rituximab, abatacept and tocilizumab. Nonetheless, the response to these treatments differs between RA patients and disease remission is only achieved in a proportion of patients and patients need to be treated chronically with often relatively expensive drugs. There is therefore a need to further improve the treatment of RA. This could be achieved by combination of different strategies. First, more optimal use of currently available treatments is needed. The use of biomarkers could play a role in optimising therapy in individual patients. For this purpose, biomarkers need to be identified predictive of the clinical response to TNF blockade and rituximab treatment. Furthermore, we evaluated repeated treatment in initial clinical responders versus non-responders to rituximab. Finally, we performed a phase 1 study with the novel B cell modulating agent atacicept.

SYNOVIAL LYMPHOID NEOGENESIS AS A BIOMARKER FOR RESPONSE TO TNF BLOCKADE IN RA. The synovial tissue of RA patients is infiltrated predominantly by macrophages and lymphocytes, but also contains dendritic cells, mast cells, natural killer cells and neutrophile granulocytes. When focussing on lymphocytes, the level of infiltration differs between patients. In some patients the tissue contains a diffuse or scarce infiltrate of T cells, while in others B and T cells are organized in lymphocyte aggregates, which are surrounded by fields of plasma cells 1. Large lymphocyte aggregates may exhibit features of germinal centers of secondary lymphoid tissue, which has been termed synovial lymphoid neogenesis (SLN). This raises the question whether they refine and amplify local humoral autoimmune responses against for instance rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA).

It has been proposed that synovial tissue with SLN forms a pathophysiologic subtype of RA, characterized by amplified local autoantibody production, associated with a more severe, aggressive disease course and differential response to therapy 2. In line with this hypothesis the presence of SLN was found to be associated with RF positive disease, the presence of erosions and rheumatoid nodules 3. However these observations were made in small patient cohorts using a selection of patients with end-stage disease. In this thesis we studied whether the presence of SLN can be used as a biomarker to identify clinically and immunological patient subsets and whether, as such, its presence can be used to predict clinical response to treatment.

In chapters 2 and 3 we analysed the relationship between SLN, humoral autoimmunity, clinical disease characteristics and treatment response in a large and representative cohort of RA patients. First, we analyzed the relationship between SLN and disease characteristics. We found that the presence of SLN is related to increased local and systemic inflammatory parameters, but it is found equally frequent in seropositive and seronegative RA patients. Furthermore, SLN was not associated with increased clinical disease activity parameters or the presence of erosive or nodular disease. We recently confirmed and extended these findings in a prospective cohort of patients with early arthritis 4. The presence of SLN was neither associated with diagnosis nor with development of persistent or erosive disease. The presence of SLN decreased over time in individual patients, which probably reflected reduced synovial inflammation after anti-inflammatory therapy or self-limiting synovitis in this particular cohort.

The presence of SLN in both seronegative and seropositive RA, as well as other forms of arthritis, suggests that SLN is a phenomenon which is not necessarily associated with autoantibodies. In line with this we recently found that even in seropositive patients the presence of SLN is not associated with an increase in local ACPA or RF production compared to other antibodies 5. Taken together, despite the fact that SLN has germainal center-like features, the data imply that SLN is rather an inflammation-driven humoral response phenomenon than a true germinal center reaction that refines and amplifies a local autoantibody response. SLN may contribute to inflammation by enhancing T cell activation, promoting local differentiation of plasma cells and by production of cytokines.

In chapter 3 we analyzed whether SLN predicts the response to TNF blockade. We found that patients with SLN overall responded well to TNF blockade and that SLN predicted clinical response independent of other known predictors, such as disease activity at baseline, the presence of ACPA and the level of synovial TNFα expression. Furthermore, we found that SLN is rapidly reversible after treatment. SLN tends to disappear already 48 hours after treatment, before a decrease in DAS28 occurs. These data suggest that TNF is involved in the formation of SLN. In line with this, previous studies showed that TNF blockade results in decreased expression of cytokines, chemokines and adhesion molecules, which are required for secondary lymphoid organ formation.

In summary, we found that SLN does not define a clinically distinct disease phenotype. Furthermore, the data suggest that while SLN exhibits some features of germinal centers it does not function as such. As an inflammation driven humoral immune phenomenon it predicts a good response to infliximab. Nonetheless, the predictive value of SLN as a biomarker of response to TNF blockade in itself is not high enough to be used as a solitary biomarker, indicating the involvement of other, as yet unknown mechanisms. Future work should expand the search for other biomarkers and molecular networks, as well as combinations of clinical variables, to achieve an effective approach that will increase the percentage of patients exhibiting a robust response to TNF blockade.
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RESPONSE.

combined with therapeutics that enhance B cell efficacy. A number of these drugs are currently under agents might be developed with increased efficacy.

response, an approach we investigated in chapter 5. Complete depletion of B lineage cells in the tissues might be achieved by repeated administration of the drug. In chapter 6 we analyzed the indirect effects of rituximab on synovial inflammatory cell populations and the differences in these populations between responders and non-responders to treatment. We found that rituximab induces a decrease in synovial T cells and disrupts the presence of SLN and follicular dendritic cells in both responders and non-responders. Furthermore, we found that rituximab induces a decrease in synovial macrophages, especially in the intimal lining layer. Finally, we found an indirect decrease (between 4 and 16 weeks after treatment) in synovial plasma cells in clinical responders. The decrease in plasma cells was correlated with the decrease in ACPA levels in peripheral blood. Of interest, we recently found that the serum levels of free light chains, plasma cell products with a half life of a number of hours, after rituximab treatment were lower in patients who did not respond to rituximab. Free light chain levels are not affected by infliximab, indicating a specific indirect effect of rituximab, through depletion of CD20 positive precursors, on short lived plasma cells that produce free light chains.

In contrast to observations in clinical responders, we found that synovial plasma cells and serum free light chains persist in non-responders to rituximab treatment. Persistence of synovial B lineage cells in non-responders to rituximab was also observed in other studies. These data suggest that patients may fail to respond to rituximab due to persistence of pathogenic B cells. We did not find baseline differences in the number of synovial B or plasma cells, the levels of RF, ACPA or free light chains in responders versus non-responders. Of note, all patients in our study were selected on the basis of being positive for RF and/or ACPA. Previous work has shown that autoantibody positive RA patients respond better to rituximab treatment than those who are autoantibody negative. Taken together, these data support the notion that autoantibody production by B cell-derived plasma cells plays an important role in promoting synovial inflammation. Conceivably, effectiveness of rituximab treatment may be increased in autoantibody positive non-responders by strategies aimed at suppression of plasma cells associated with autoimmunity in the tissues.

In chapter 7 we studied the relationship between the response to rituximab and the type I interferon (IFN) signature in peripheral blood mononuclear cells (PBMCs). The type I IFN signature is found in a subset of RA patients as the dominant signalling signature in PBMCs. It is also found in a proportion of patients with other autoantibody associated autoimmune diseases, such as Sjögren’s syndrome, multiple sclerosis, dermatomyositis, type I diabetes mellitus, systemic sclerosis and systemic lupus erythematosus. Rituximab has shown to be clinically efficacious in many of these conditions. In the two cohorts that we studied rituximab was less effective in RA patients with the IFN signature. These data suggest that the type I IFN signature might be used to predict beforehand which patients will benefit most from rituximab treatment. Still, the predictive value of the type I IFN signature in itself was not sufficient to be used as a solitary biomarker. Therefore, the type I IFN signature should be assessed in future studies in combination with other biomarkers for its validity to guide rituximab treatment decisions.

In chapters 8 to 10 we studied the current treatment schedule of rituximab, which consists of a course of 2 times 1,000 milligram of rituximab. In B-NHL patients rituximab is less efficacious in patients with a large tumor mass and rituximab levels are lower after therapy. In chapter 8 we analyzed whether we could find a similar relation in RA. We found that rituximab levels were not related to the extent of B cell depletion after treatment, or to clinical response. We also found that clinical response was not significantly lower in patients who formed anti-rituximab antibodies. These data indicate that the current rituximab treatment regimen results in drug levels that are in the therapeutic range in both responders and non-responders to treatment, even when patients form anti-rituximab antibodies.

In chapters 9 and 10 we studied the effects of repeated treatment with rituximab in initial responders and non-responders to treatment. In our cohort, initial non-responders did not respond to re-treatment, while clinical responders had an improved response to a second treatment course. Our findings have recently been confirmed in a large, randomized clinical trial. Other studies, however, have suggested that seropositive patients who fail to respond to a first course of rituximab may still respond to a second course. In light of the availability of other therapeutic options, for individual patients who are rituximab non-responders other treatment options should be considered.

Chapter 11 describes the results of a phase Ib trial with atacicept in RA patients. Atacicept is a recombinant fusion protein that binds and neutralizes the activity of the cytokines B lymphocyte stimulator (BlyS) and A proliferation-inducing ligand (APRIL) and the heterodimer of these 2 cytokines. BlyS and APRIL enhance B cell survival, proliferation, antigen presentation, and class-switch recombination at various stages of B cell development. We found that atacicept is well tolerated with an in vivo biologic effect consistent with its mechanism of action. Treatment resulted in a decrease in serum RF and ACPA levels in parallel with total serum immunoglobulin levels. Future work will need to address whether this biological effect might translate into clinical efficacy.
CONCLUDING REMARKS AND FUTURE DIRECTIONS. In this thesis we investigated B cells and B cell-directed therapy in RA. We aimed to find biomarkers predictive of the clinical response to TNF blockade and rituximab, identify immune mechanisms that remain active in patients not responding to therapy, and investigate the effect of systematic retreatment in initial responders versus non-responders. Finally, we conducted an exploratory study on the effects of atacicept in RA. The results presented here support the notion that RA is a heterogeneous disease with a variable response to a given therapy and indicate that specific biomarkers may predict the response to therapy. The persistence of B lineage cells in the synovium of autoantibody positive RA patients who do not exhibit a robust response to the first cycle with rituximab suggests that novel approaches may be needed to interfere with these cells in initial non-responders.

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