Anti-TNF therapy in rheumatoid arthritis: Searching for mechanisms of effect
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General discussion and summary
This thesis aims to improve our knowledge of different aspects of TNF blockade in rheumatoid arthritis (RA) by studies of its mechanism of action, predictors of response and the effects on quality of life and ability to work.

BACKGROUND

RA is a chronic systemic autoimmune disorder characterized by synovitis and progressive damage to articular cartilage and subchondral bone in the majority of patients. Besides these well known effects on the joints, during recent years it has become evident that RA patients have an increased cardiovascular risk. Traditional cardiovascular risk factors in combination with the inflammatory status in RA patients contribute to the high prevalence of cardiovascular disease in RA and both risk factor management and adequate treatment, reducing inflammation, are recommended. In addition, RA has major individual and socio-economic consequences. For the individual patient it often leads to loss of work with loss of income as a consequence. For society there are direct (i.e., healthcare) costs and indirect costs, involving factors such as worker absence, reduced productivity due to disability, and early retirement.

The etiology of RA is not completely understood. The combination of genetic susceptibility, with environmental factors may lead to the development of this disease. Smoking is a well established environmental factor in the pathogenesis of ACPA positive RA. Recently, periodontitis was also found to be associated with the development of RA. Both may promote post-translational modifications, through peptidyl arginine deiminase, type IV (PADI4), resulting in citrullination of mucosal proteins and loss of tolerance to neoepitopes that can subsequently elicit an ACPA response. In addition, our group has shown that also obesity is significantly associated with the development of arthritis in auto-antibody positive individuals and that it is associated with a diminished clinical response to anti-TNF treatment with infliximab in established RA patients. This suggests the involvement of white adipose tissue in the pathophysiology of RA, which may partly be the result of the so called adipokines. These pro-inflammatory factors secreted by white adipose tissue have been shown to be involved in the modulation of inflammation and the innate immune system.

In recent years, the treatment of RA has greatly improved, partly due to the introduction of a new class of drugs, the ‘biologics’. They specifically aim at a single target within the dense network of inflammatory cells and cytokines driving RA, which may ultimately reduce inflammation entirely. Currently, four classes of biological are frequently used in the treatment of RA: anti-TNF therapy (infliximab, adalimumab, etanercept, golimumab and certolizumab), anti-B cell therapy (rituximab), modulation of co-stimulation between T cells and antigen presenting cells (abatacept) and anti-interleukin-6 receptor antibody therapy (tocilizumab). After failure of DMARD treatment, patients often start with anti-TNF therapy as a first line biological in light of the vast experience with this class of drugs. If treatment with TNF-antagonists is not effective, patients are switched to another TNF-blocking agent or another drug. This can be a time consuming process, since it often takes at least three months to evaluate clinical response. In addition, the use of biologics is associated with considerable costs and side effects. Thus, the
identification of patient subgroups that will respond to a certain drug over drugs with a different mechanism of action would have several advantages. Obviously, patients would benefit from the direct start of effective therapy thereby lowering disease activity and halting progression of damage to the joints. Conceivably, this could also translate into reduction of cardiovascular risk. Next, it would improve cost effectiveness and it would avoid unnecessary exposure to side effects in patients who are unlikely to respond to a specific mechanism of action.

Though anti-TNF therapy is approved and widely used in clinical practice, its specific mechanisms of effect are still not entirely understood. Previously, infliximab treatment has been shown to result in marked reduction of synovial inflammation as early as 24-48 hours after infusion, which could not be attributed to induction of apoptosis. Therefore, reduced synovial cell counts at an early time point after TNF antagonist treatment could perhaps be explained by modulation of cell migration. The effect of TNF blockade on several cytokines, chemokines and adhesion molecules could reduce influx of inflammatory cells. Similarly, the decrease of these cytokines, chemokines and adhesion molecules could also facilitate egress of cells from the synovium into the lymphatic draining system.

The study of biosamples and patient reported outcomes obtained before and after initiation of TNF blockade may provide further insight into the specific mechanism of action as to how anti-TNF treatment leads to clinical effectiveness. This will ultimately help our understanding of the reasons as to why patients respond or not respond and improve the effectiveness of current treatment.

**MAIN FINDINGS**

The decrease in macrophage numbers in the synovium has been associated with clinical improvement after effective treatment. Previously, this could not be explained by apoptosis induction at the site of inflammation leaving either reduced cell influx or enhanced cell efflux to explain this process. In chapter 2 we investigated the effect of anti-TNF therapy on macrophage infiltration into the synovium. Using a novel imaging technique to visualize the migratory behavior of autologous monocytes, we found that CD14+ monocyte influx into the synovium is not decreased two weeks after the start of adalimumab treatment, whereas there was already significant clinical improvement at this early time point. Based on these data we hypothesized that the decrease in expression of adhesion molecules and chemokines in the tissue may facilitate macrophage egress from the synovium, resulting in decreased macrophage numbers in the synovial tissue. In line with increased cell egress after anti-TNF treatment, we previously found that anti-TNF therapy results in increased lymphatic vessel formation in the synovium. In chapter 3 we studied the changes in the T-cell repertoire shortly after initiation of infliximab treatment. In addition, we further explored the concept of cellular egress from the synovium as a result of anti-TNF therapy. To our knowledge there are no studies showing that macrophages might recirculate into the peripheral blood and become monocytes again, whereas this has been shown for T cells. Our group has developed a new technique, using next generation sequencing, that could provide an accurate quantitative data on the degree of expansion of individual T cell clones within the complete T-cell receptor (TCR) repertoire,
allowing quantitative comparisons of clonality between different patients and between different compartments of the body. Using this technique, we found that infliximab therapy lead to a depletion of dominant clones present in the synovial tissue and peripheral blood of RA patients within 48 hours after infliximab infusion, which might help explain the disease-modifying properties of this treatment. Previously, we did not find increased apoptosis in the synovial tissue and peripheral blood and did find increased lymphatic vessel formation in the synovium after infliximab therapy. Based on these studies we hypothesized that clones from both the synovium and peripheral blood might move to the lymphatic system after infliximab therapy. We could only detect a small percentage of synovial specific T cells (i.e. TCR sequences that could not be detected in peripheral blood at baseline) in the peripheral blood 48 hours after infliximab infusion. This suggests that if egress from the synovium occurs after infliximab infusion, there is retention or apoptosis induction of T cells in the lymphatic system after egress from the synovium and only few T cells recirculate into the peripheral blood. Of note, the effects of TNF inhibition may in part differ on T cells versus monocytes, and we cannot exclude the possibility that infliximab therapy also results in a decrease influx of T cells into the synovium.

Several studies aimed at identification of predictors of response have looked into demographic, clinical and radiological parameters: genetic markers, soluble biomarkers measured in peripheral blood, and synovial markers (reviewed in). However, at this point these associations are not strong enough to be translated into a predictive test in individual patients. Recently, we have developed a model that can partly predict response to TNF blockade in RA patients. The addition of variables to this model may increase the prediction of response. In chapter 4 we found that patients with higher synovial CD11c expression and higher DAS28 levels at baseline respond better to infliximab therapy than patients with lower synovial CD11c expression and lower DAS28 levels at baseline. Although our results await confirmation in a larger cohort, this study suggests that CD11c is an interesting candidate to further refine this prediction model, ultimately leading to a prediction model with sufficient positive and negative predictive value to be used for treatment decisions at baseline in the individual patient. Of note, in peripheral blood higher expression levels of CD11c+ were associated with higher expression levels of inflammatory markers in monocytes. In agreement with this, we have previously reported that responsiveness to infliximab treatment is related to pre-treatment tissue inflammation. Anti-TNF therapy has well-established beneficial effects on disease activity, joint damage and cardiovascular disease, although the exact mechanism by which TNF blockade could reduce cardiovascular disease risk remains to be elucidated. There is increasing evidence that adipokines may exert pro-inflammatory and destructive effects in RA and have a role in cardiovascular disease in RA patients. In chapter 5 we report the effect of adalimumab and glucocorticosteroids on adipokine serum levels (adiponectin, leptin, resistin, visfatin and vaspin) in relationship to inflammation, radiological changes and lipid profile in three cohorts of RA patients. Interestingly, there were both similarities and opposing effects of treatment with adalimumab or glucocorticosteroids on adipokine serum levels. Adalimumab treatment and treatment with glucocorticosteroids showed opposing effects on vaspin and visfatin serum levels. Vaspin serum levels increased after glucocorticosteroid treatment, but did not change.
after TNF blockade, whereas visfatin serum levels did not change after glucocorticosteroid treatment and decreased after TNF blockade. Previously, increased visfatin levels have been independently associated with an increase in cardiovascular disease disease and increased vaspin levels are associated with decreased insulin sensitivity, which is commonly seen after glucocorticosteroid treatment. Therefore, the increase in vaspin serum levels after glucocorticosteroid treatment and the decrease in visfatin levels after TNF blockade could both partly explain the different effects on cardiovascular risk associated with these treatments.

In line with this, we also found that in the adalimumab cohort, the decrease in visfatin levels correlated with the improvement in lipid profile independent of the decrease in CRP, suggesting a role for visfatin specifically in the improvement of the lipid profile independent of disease activity. On the other hand, there were also similarities in the effects of anti-TNF treatment and treatment with glucocorticosteroids on changes in adipokine serum levels. After several weeks either treatment had an effect on adiponectin or leptin serum levels, suggesting that these adipokines are not involved in the reduction of inflammation, bone damage and atherogenesis after TNF blockade. In addition, both treatment strategies decreased resistin levels, which was associated with the decrease in ESR in both cohorts, in line with resistin’s proinflammatory regulatory functions. Furthermore, in the adalimumab cohort resistin levels at baseline were predictive of radiological damage at baseline, independent of ACPA status or CRP levels. Overall, these data support a role for resistin and visfatin in the pathophysiology of RA.

Chemerin is a novel adipocytokine and chemokine involved in the recruitment of dendritic cells and macrophages and was recently found to be expressed by cells in the synovial tissue. In chapter 6, we found that chemerin serum levels are reduced after adalimumab treatment, and that the decrease in chemerin serum levels was associated with clinical improvement, as shown by a decrease in DAS28, ESR, CRP, IL-6, and MIF. As these mediators are produced by macrophages and their reduction might be a consequence of decreased chemerin-dependent accumulation of synovial macrophages. This suggests a possible distinct role for chemerin in the migration and/or retention of macrophages in the synovium and as such in the pathophysiology of RA. In addition, our data suggest that smoking might elevate chemerin serum levels. In RA cigarette smoking is a well-recognized risk factor for the development of the disease and it has also been associated with more severe disease. Thus, elevated expression of chemerin might represent one of the underlying mechanisms by which smoking increases disease activity in RA patients, and could represent a novel therapeutic target.

RA clearly has a major economic impact on society. In a review of literature, the mean annual costs per patient were estimated at around €13,500 in Europe. Besides medical costs and costs associated with drugs, which account for about one-third of these costs, productivity losses account for a substantial part of the total costs of RA (32%). In chapter 7 we have shown that work ability, quality of life, and fatigue in patients with established RA clearly improved after 1 year of adalimumab therapy. This suggests that, although biological treatment clearly increases direct costs, it can decrease the indirect costs. And indeed in economic analyses, incorporating indirect costs, biological treatments appear to provide sufficient cost effectiveness. Previously, work ability has been shown to be predictive of return to work. However, in our
study the increase in work ability was not translated into actual return to work. This might be explained by a need for a longer follow-up. In line with this notion, a recent study in patients diagnosed with cancer revealed that work ability predicted the return-to-work rate 18 months after the first day of sick leave. In addition, there might also be a need for the development and implementation of return-to-work programs for RA patients. We are currently awaiting the results of a randomized controlled intervention programme aimed at improving functioning at work. If the intervention program will be (cost)effective, substantial improvements in work productivity might be obtained among workers with RA at lower costs.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In this thesis we studied the mechanism of effect of TNF blockade in RA. We aimed to clarify how TNF blockade leads to the marked decrease of synovial cellularity early after initiation of treatment. In one study presented in this thesis we did not find a decreased influx of monocytes into the synovium after anti-TNF antibody treatment. Previously, we have shown that anti-TNF treatment does not appear to directly induce apoptosis in vivo, but we did observe reduced cellularity and increased lymphatic vessel formation in the synovium after infliximab therapy. Taken together, these data led to the hypothesis that the decrease of cytokines, chemokines and adhesion molecules after the initiation of TNF blockade facilitates egress of cells from the synovium into the lymphatic system. Further research could address this by examining the lymphatic system after TNF blockade e.g. by lymph node biopsies. In addition, the use of other novel imaging techniques, such as tracking of labeled macrophages by PET could provide more insight.

In addition, studying the effects of anti-TNF treatment on recently discovered molecules that might be involved in RA pathogenesis, such as adipokines, could add to our knowledge on the pathogenesis of RA and on the exact mechanism of action of anti-TNF treatment. This might facilitate our understanding of the reasons as to why patients are responders or non-responders to TNF blockade, making it possible to identify biomarkers predictive of response. Ultimately, this could lead to treatment regimens, aiming for disease remission without avoidable side effects and with optimal cost-effectiveness.

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