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Summary and Discussion

Introduction

The aim of this thesis was to investigate whether arthritis development can be predicted in persons at risk for developing rheumatoid arthritis (RA) and whether disease onset can be prevented or delayed in these “at-risk” persons. This would imply a paradigm shift in rheumatoid arthritis (RA): to initiate intervention strategies in those individuals at risk before the actual onset of clinically detectable arthritis. Early treatment of (rheumatoid) arthritis seems to result in a greater than usual response to therapy with sustained benefit (the ‘window of opportunity’).^{1,2} Despite these efforts, a large proportion of patients presenting with early, active, RA still show erosions at baseline² and in 36-54% of cases, patients attending arthritis clinics shortly after the onset of symptoms already have joint damage that is visible radiographically.³⁻⁵ Therefore, targeting even before the onset of arthritis in patients at risk for the development of RA seems a conceivable next step in prevention of RA associated disease burden. Despite growing knowledge on the genetic, environmental and immunological events preceding rheumatoid arthritis, targeting patients in the preclinical phase has not been attempted previously.

Effect of anti-TNF treatment on autoantibodies. To extend current knowledge on ACPA as disease specific marker and IgM-RF as marker of rheumatoid inflammation, the effects of anti-TNF treatment on auto-antibody levels in active RA patients were studied and the results are reported in chapter 2-4. Previous studies had reported controversial results, probably due to the small sample size and patient selection. Most studies show a decrease in IgM-RF and some also in ACPA levels, whereas a relationship with disease activity and acute phase reactants, as well as subclass distribution had not previously been studied. Chapter 2 confirmed previous observations that IgM-RF decreases with ~50% and ACPA with ~25%, irrespective of the assay used for measuring ACPA (anti-CCP or ACF). Furthermore, the decrease in IgM-RF is greater than that of ACPA. Patients also turn negative for IgM-RF and the decrease in IgM-RF, but not ACPA, is associated with the observed decrease in acute phase reactants and disease activity score (Chapter 3). Despite the minor response of ACPA during anti-TNF treatment, the IgG4 ACPA subclass decreases significantly more than IgG1 ACPA, suggesting that the effect of anti-TNF on ACPA is not well mirrored by total IgG APA levels. Furthermore, it suggests that an IgG1:IgG4 shift occurs during anti-TNF treatment reflecting abrogation of chronic antigenic stimulation by citrullinated proteins during anti-TNF treatment, leading to decreased IgG4 ACPA levels (Chapter 4).

Relationship between age at ACPA seroconversion and duration of preclinical RA period. Using serial blood samples of patients who later developed RA, we showed that the age at seroconversion of ACPA, but not IgM-RF, is correlated to the period until the onset of RA related symptoms, i.e. younger age was associated with shorter period of ACPA positivity until the onset of symptoms (Chapter 5).

Risk assessment in autoantibody positive arthralgia patients. In Chapter 6-8 we reported whether arthralgia patients resemble arthritis patients and if arthritis development could be predicted in arthralgia patients. Therefore, starting in June 2004, arthralgia patients positive for ACPA and/or IgM-

RF are prospectively followed and arthritis development is monitored. 250 patients have currently been included; the median follow-up duration is more than 2 years.

Comparing baseline SE status and ACPA levels in ACPA positive arthralgia patients, early arthritis and established RA patients, we observed a higher frequency of SE positivity in arthralgia patients compared to population based results, but a lower frequency when compared to RA patients (Chapter 6). Furthermore, SE positivity was associated with higher ACPA levels in arthralgia patients, but not in (early) RA patients. These data indicate that, compared to SE-positive patients, SE negative patients as a group go through a longer arthralgia phase, or alternatively have a lower risk for transition from ACPA positive arthralgia to RA. Furthermore, these results suggest that in this early stage the effect of the SE on disease risk may be mediated through higher ACPA levels.

The effect of ACPA and the SE on arthritis development was prospectively studied in Chapter 7. Previous work using retrospective data of preclinical RA patients had estimated the chance of developing RA in the presence of IgM-RF and/or ACPA without arthritis at 2% in the general population up to 44 % in a high risk population, defined as two first-degree relatives with RA⁶. Our prospective data show that the hazard for ACPA positive (\pm IgM-RF positive) arthralgia patients is 6 when compared to IgM-RF positive, ACPA negative patients, with 27% of ACPA positive arthralgia patients developing arthritis after a median follow-up of approximately 2 years. This risk increases with the concomitant presence of IgM-RF (40%) and high ACPA levels, but not the SE.

In chapter 8, peripheral blood gene expression profiling was used to identify additional biomarkers for the development of arthritis in arthralgia patients. These data revealed remarkable heterogeneity in arthralgia patients, with part of the gene expression profiles discovered resembling that of RA patients. These profiles were indeed predictive of arthritis development, independent of ACPA status, providing a rationale for the use of gene expression profiling in risk assessment strategies.

Taken together, these data suggest that a combination of ACPA, IgM-RF and gene expression profiling may be able to predict future arthritis onset in arthralgia patients.

Dexamethasone in the primary prevention of RA. In Chapter 9 the results of a randomized, placebo-controlled trial of dexamethasone in the primary prevention of RA are described. Intramuscular dexamethasone in autoantibody positive arthralgia patients leads to a significant decrease in ACPA levels, and to a lesser extent IgM-RF levels, after 6 months, but does not delay or prevent arthritis development after 19 months. ACPA dynamics may have important prognostic consequences for the development of (rheumatoid) arthritis. Follow-up may shed light on the long term effects of this early intervention strategy in antibody positive arthralgia patients.

Concluding remarks and implications for future research

This thesis contributes to the wealth of knowledge currently available on the role of autoantibodies, especially antibodies to citrullinated proteins (ACPA), in (the preclinical phase of) RA.

Previous research has shown that (I) ACPA are highly specific for RA, (II) interact with the major genetic risk factor for RA (the 'shared epitope'), (III) are present in the preclinical phase of the disease,

(IV) induce arthritis in rodents and (V) are only moderately modulated by aggressive anti-rheumatic treatment.⁶⁻¹¹ This thesis adds several observations to these data. First, ACPA and IgM-RF are two distinct autoantibody systems, in the clinical and also in the preclinical phase of RA. ACPA responds less to anti-rheumatic treatment than IgM-RF and IgG4 ACPA is preferentially modulated, possibly reflecting the role TNF blockers may exert on chronic antigenic stimulation by ACPA. Furthermore, changes in IgM-RF are associated with disease activity, whereas ACPA changes are not. These results underscore the current view that ACPA is a disease-specific marker, whereas IgM-RF acts primarily as disease activity marker.¹²

Prospective follow-up of the arthralgia patients confirmed this: arthritis development was more frequent in ACPA positive patients when compared to ACPA negative arthralgia patients. IgM-RF contributes to disease risk, but in ACPA positive patients only. In arthralgia patients, the effect of the SE on arthritis development is probably mediated by ACPA, as was suggested in a cross-sectional study of arthritis and arthralgia patients, and confirmed by prospective follow-up of these patients. Strikingly, ACPA is modulated effectively in the preclinical phase, and in contrast to the clinical phase, the effect of twice dexamethasone on ACPA seems even greater than on levels of IgM-RF. This strategy however does not prevent or delay arthritis development.

Questions raised for future research. Since still only ~20% of ACPA and/or IgM-RF positive arthralgia patients develop arthritis after 2 years of follow-up, predictive power needs to be increased before future intervention strategies can be initiated. This thesis has already shown that gene expression profiles of peripheral blood may further increase disease risk in ACPA positive patients, but additional risk enhancers will have to be explored as well, ideally leading to a prediction model including those factors accurately predicting the risk of arthritis development in the near future. To develop this prediction model, autoantibody positive arthralgia patients are continuously being included in the prospective cohort study and known and unknown risk factors for RA, but also methods for the detection subclinical synovitis/inflammation will be investigated in these patients. For instance, one of the remaining questions is the existence of ACPA epitope spreading; i.e. is the immune response in ACPA positive patients initially directed against one citrullinated protein and does this response broaden towards onset of arthritis?

Since twice dexamethasone leads to a specific and sustained decrease of ACPA (and IgM-RF) but does not delay or prevent arthritis development in arthralgia patients, other therapeutic regimens are needed to successfully intervene in the early phase of the disease. Two options are possible, one is a shift from the initiation of 'traditional' DMARDs, combination strategies or 'biologicals' (such as anti-TNF treatment or B-cell depletion therapy with rituximab) to the preclinical phase, the other is the development of new therapeutic strategies to target ACPA before clinically manifest arthritis appears. B-cell depletion seems an attractive option since it has been shown that autoantibodies decrease during rituximab treatment and arthritis returns only after B cells and autoantibodies have returned to the circulation. It leads to rapid and sustained clinical remission, only needing treatment when symptoms reappear.^{13;14} However, the longterm safety of B cell depletion is not yet established and remains a concern when used in patients who do not yet have arthritis.

One could also envisage an approach similar to the BeSt protocol in RA,² with arthritis development instead of RA-remission as key determinant in initiating the next treatment step. Repeated corticosteroid injections may also delay/prevent arthritis onset, but steroid-induced side-effects will probably soon outweigh the benefits.

Ideally, new therapeutic strategies aimed at inducing tolerance for citrullinated proteins before the onset of disease have to be developed using the immunodominant citrullinated peptides. The proof of principle has elegantly been shown by Kuhn et al, who reported partial protection of collagen-induced arthritis by inducing tolerance by intravenous administration of a citrulline-containing peptide in mice.⁸ These mice also showed reduced antibody responses to citrullinated proteins and decreased epitope spreading to citrullinated and native epitopes. Furthermore, monoclonal antibodies to citrullinated peptides enhanced arthritis and the protective effect of tolerization with citrullinated peptides is overcome by administering these antibodies, leading to redevelopment of severe arthritis. Currently, four different protocols are employed for inducing peptide-specific immune tolerance (reviewed by Miller et. al.¹⁵). In general, peptide-specific tolerogenic strategies have led to protection of induction, but not suppression of auto-immunity in rodents, but several trials of disease suppression in humans (for instance oral insulin in diabetes mellitus type 1¹⁶) have not paralleled these successes and non-antigen-specific therapeutic approaches have been far more successful in the treatment of autoimmune diseases. However, since breakdown of tolerance for citrullinated proteins is the hallmark of (ACPA positive) RA, induction of tolerance to these peptides before disease onset may still truly be the 'holy grail' in rheumatology.

Key points:

- IgM-RF preferentially decreases and parallels the acute phase response during anti-TNF treatment in RA, whereas the decrease in ACPA seems greater in arthralgia patients in response to dexamethasone.
- IgM-RF and ACPA decreases only in those RA patients responding to anti-TNF treatment.
- The response of ACPA during anti-TNF treatment in RA is better mirrored by the IgG4 subclass.
- Younger age at ACPA seroconversion is associated with shorter duration of ACPA positive asymptomatic period.
- ACPA positivity is strongly associated with future arthritis development in arthralgia patients, this risk is enhanced by the presence of the IgM-RF, high ACPA levels and specific gene expression profiles.
- Twice dexamethasone intramuscular modulates ACPA and IgM-RF levels, but does not prevent or delay RA onset in arthralgia patients.

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