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Systemic sclerosis: are anti-nuclear antibodies our guiding stars?

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PART IV

Systemic Sclerosis: are auto-antibodies our guiding stars?

8

Summary and discussion

In this thesis the role of anti-nuclear auto-antibodies to function as biomarkers in Systemic Sclerosis (SSc) has been evaluated. Respectively, the heterogeneity of the disease, the need for biomarkers and the role for auto-antibodies as such, with specific attention for anti-topoisomerase have been outlined in this thesis.

SSc, is a complex heterogeneous connective-tissue disease that can have a mild disease course, but can also be life-threatening (1). A general introduction on SSc, with discussion of its epidemiologic characters, history, discussion on pathogenesis, diagnosis and classification and treatment is given in Chapter 1. In this chapter also a brief introduction on the Leiden Comprehensive Care Pathway and de Combined Care In Systemic Sclerosis (CCISS) cohort are given, which has been the basis for all research performed within this thesis.

The need for biomarker research

Risk-stratification in SSc is difficult. Exemplary is the disease course of the placebo group in the RITuximab in Systemic sclerosis trial (RITIS-trial) in **Chapter 2.** The trial aimed inclusion of patients at high risk for deterioration, however, was not able to select cases with significant deterioration.

The RITIS trial was a study in which 16 early SSc patients (time of diagnosis <2 years prior to inclusion) were randomized 1:1 to treatment with rituximab (an anti-CD20 B-cell depleting agent) or placebo. As in new-born tight skin mice anti-CD20 treatment development of fibrosis was prevented, while in adult tight-skin mice with already established disease there was no effect of treatment (1), rituximab was hypothesized to terminate the disease process and to have a beneficial effect only in early disease stages. Unfortunately, the trial observed no significant effects. This however does not exclude that some patients may have had a beneficial effect of the treatment with rituximab. Because of the rarity of the disease, performing large scale trials are difficult. In order to study treatment effect in a group as small as possible, selection of patients in which the greatest effects are likely to be observed is required. For a treatment agent that was hypothetically able to stop the disease process and not able to heal, an appropriate selection of patients would imply deterioration in the placebo group. However, as shown from the disease course of the placebo group in the RITIS trial, in which skin scores, lung function and daily functioning were all rather stable, such selection is challenging.

The RITIS trial is not the only trial in SSc that suffers from poor patient selection because of inability to predict patients with progressive disease. For example, the first Scleroderma Lung Study (2) and the Focussced trial (3) showed a relative stable disease course for placebo treated patients. As shown by Table 1 from Chapter 1, SSc-specific auto-antibodies are associated with specific disease features in SSc. Based

on these findings from cross-sectional research, various authors have suggested that auto-antibodies can be used to predict disease course of SSc patients (4-6). The RITIS trial, the SLS I study and also the Focussced did not employ auto-antibodies for patient selection in their inclusion criteria. In our thesis we tried to answer if employment of auto-antibodies for inclusion criteria in such studies should be performed.

Auto-antibodies as biomarkers in Systemic Sclerosis

In **Chapter 3** we evaluated the attributive value of that auto-antibodies in survival prognostication. For this goal we performed a statistical analysis (hierarchical clustering in combination with principal component analysis), in which we let the computer make subgroups of patients based on respectively clinical and demographic characteristics only and subsequently performed the same analysis, only with additional use of auto-antibody status to simulate risk-stratification. Comparing risk-stratification with and without knowledge of auto-antibodies showed that correct prediction of survival within five years increased when the antibody subtypes were included in the model. However, also the number needed to screen increased with 27%, while correct identification of high-risk individuals increased with 13%. This illustrates that although auto-antibodies may associate with survival, its contribution to clinical prognostication when it comes to survival is limited.

Some auto-antibodies in SSc have been described to associate with concurrent malignancies. This is especially the case for RNA polymerase III (RNApIII) (7-9). Therefore, In current disease management, when a patients is newly diagnosed with RNApIII+ SSc, a malignancy screening is performed. For other auto-antibodies their relationship with coincident malignancies is less clear. Bernal-Bello et al. suggested that Pm/Scl antibodies in SSc could also be related to an increased malignancy risk. In **Chapter 4** we show that we could not confirm this finding in the CCISS cohort. Pathophysiologically, the relationship between SSc and cancer might be based on epitope spreading of an immune reaction that was primarily targeted at a transformed oncogene auto-antigen. However, presence of continuous inflammation might also create a situation in which DNA damage more easily emerges with development of cancer as a consequence.

In conclusion, these studies confirm that auto-antibody status only cannot function as an appropriate biomarker in SSc. The urge for a biomarker however is present, not only to select the right patients for clinical trial participation, but also to be able to identify the right patients to monitor more or less closely. Most of these patient will have an anti-topoisomerase I auto-antibody. However as discussed below, within this group further stratification is needed.

Anti-topoisomerase I positive systemic sclerosis

We explored the heterogeneity of ATA positive SSc in **Chapter 5.** We showed that as expected, ATA+ patients in the CCISS cohort more often develop severe pulmonary fibrosis and diffuse skin thickening. Interestingly, when analysed from the time of inclusion in our cohort, in contrast to what one might expect, there was no difference between ATA+ and ACA+ patients in the amount of – and time to disease progression and survival. We were not the first to notice this, also Steen et al. already in 1988 had noticed that when analysed from disease onset, there is a clear difference in survival between ATA+ and ACA+ patients, while survival between ATA+ and ACA+ is similar when assessed from their initial visit to a specialized SSC clinic (10). Although this was recognized in 1988, with the coming of the ACR/EULAR 2013 SSc classification criteria from which is thought to enable diagnosis of patients in an earlier stage (11, 12), we expected that the current clinical practice would be more in line with the analysis from disease onset in 1988. Our analysis revealed that this was however not the case. It seems that the ACR/EULAR 2013 SSc criteria mainly enable diagnosis of mild and not early disease. This became even more clear, by the observation that of all ATA+ patients with longitudinal follow-up ranging up to 8 years, a third of patients never developed fibrotic complications. Additionally, ATA+ patients with normal lung function test at first screening were unlikely to deteriorate to severe lung disease during follow-up. The heterogeneity of ATA+ SSc is as such clearly demonstrated, with a large deal of ATA+ disease under the 2013 criteria being mild.

In SSc, it is remarkable that while the disease is far more prevalent in women, male patients more frequently harbor ATA. We therefore evaluated the prognostic implications of ATA+ and ACA+ separately in men and women in **Chapter 6**. Herein we found that sex is not only associated with the auto-antibody subtype, but is also an independent contributor to disease severity in SSc. Males have increased chances for development of diffuse cutaneous involvement, pulmonary hypertension and disease related mortality. Intensified screening therefore seems adequate in all male SSc patients, independent of auto-antibody status.

In an attempt to recognize when to be alarmed in ATA+ SSc, we investigated whether knowledge of isotypes could be of help to identify patients likely to deteriorate in **Chapter 7.** IgM is an isotype, known to occur in active phases of many diseases. Our finding that ATA-IgM is associated with disease progression, for us therefore confirmed that knowledge of isotype status of specific ANA in SSc might function as additional biomarker. Presence of ATA IgM likely reflects ongoing presentation of disease relevant autoantigens with recruitment of short-lived naïve B cells. But as also part of ATA-IgM+ SSc patients do not deteriorate, there is an ongoing research to factors that lay behind being ATA-IgM+ and that do explain why some patients have stable disease, while others develop these life-threatening complications.

Future perspectives on research in Systemic Sclerosis

Our lack of understanding the disease mechanisms in SSc, hampers the development of successful therapies and cost-effective screening programs. In my opinion, future research therefore should focus on increased understanding of the disease and elucidation of the exact mechanisms that lead to the heterogeneous clinical picture of SSc.

One possibility in to gain better understanding of disease pathophysiology could be the study of patients in clinical remission. As discussed in **Chapter 1** three major contributors in disease pathogenesis of SSc exist: microangiopathy (13, 14), fibrosis (15-18) and immunological changes (19-21). Studying the changes in these three compartments after HSCT might be key to understanding disease mechanisms in SSc.

Another strategy that could provide us with increased understanding of SSc are the clinical trials that are conducted world-wide. Multicenter research, including many patients, do not suffer from insufficient power. Knowledge of the drug-target of the ligand that is tested in a trial with beneficial effect could shine light on disease etiology and equips the treating rheumatologist with strategies in a disease where until know physicians are more or less powerless. For an academic center like the Leiden University Medical Center, being able to participate in trials like the FASST (lanifibranor)(22), and RESOLVE (lenabasum)(23) is therefore priceless.

Biomarkers in Systemic Sclerosis: Are auto-antibodies our guiding stars?

In conclusion, auto-antibody status alone does not provide us with sufficient information to perform risk-stratification in such a way that we can either select the right patients for clinical trials, construct a tailor-made screening program for patients or decide whether and which therapy to start. Still, there are many stumbling blocks ahead in achieving these goals. Nevertheless, we do know that auto-antibodies are clearly associated with the phenotype of the disease. Therefore auto-antibodies might function as one of the guiding stars in SSc follow-up and treatment. However, we are still searching for the total picture in help of navigating. Let's hope, that unlike at the time of Klee (the painter of the work on the cover of this thesis, which represents his work "This star teaches bending" – 1940), in the near future we will no longer have to bend for the star of SSc, but find stars that help us navigate safely through the sometimes calm and peaceful, but possibly also dangerous and unpredictable sea, which the disease course of SSc still is.

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