Antibodies against antibodies: immunogenicity of adalimumab as a model
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ENGLISH SUMMARY

Therapeutic monoclonal antibodies are effective drugs for many different diseases. However, in part of the patients the therapeutic monoclonal antibody is recognized by the patients’ immune system, leading to the formation of antibodies against the drug. The production of these anti-drug antibodies (ADA) has been linked to lower functional drug levels and reduced clinical response. One of these drugs is adalimumab, a fully human monoclonal antibody directed against TNF which is used for the treatment of different auto-immune diseases such as rheumatoid arthritis (RA). Previously a variety of studies have focused on the clinical aspects of immunogenicity of adalimumab, in this thesis we focused on more immunological aspects of this immune response.

In chapter 2 we have investigated the role of IgG subclasses in the immune response against adalimumab. Although IgG4 represents a minor fraction of total serum IgG, long term exposure to antigens has been previously described to result in antigen-specific IgG4 production. Therefore it may be expected that long term exposure to adalimumab might lead to the production of specific IgG4 antibodies. To investigate this we measured total ADA and IgG4 ADA in a cohort of 271 consecutive RA patients during 3 years of treatment. Results show ADA production in 32% of the patients and IgG4-ADA in 29% of the patients. The proportion of IgG4 of total IgG against adalimumab varies between patients and in some patients we found that a significant part of the antibodies is of the IgG4 subtype.

In the detection of ADA drug interference is a major complication. In most assays ADA can not be detected while in complex with adalimumab. Therefore ADA can only be detected if ADA production exceeds drug levels in the patients’ serum, leading to an underestimation of ADA production. In chapter 3 we describe a novel assay for the detection of ADA which allows measurements in the presence of high drug levels. The pH-shift-anti-Idiotype Antigen binding test (PIA) is based on acid dissociation of ADA-drug complexes and on blocking the reformation of these complexes by addition of an excess of rabbit anti-idiotype-f(ab) before neutralization. Afterwards released ADA can be detected in the regular antigen binding test (ABT).

In chapter 4 we use the PIA for the detection of ADA in a group of 99 adalimumab-treated RA patients during 3 years of treatment. We detected ADA in 53 patients. In 50 of these patients ADA could already be detected within the first 28 weeks of treatment. Patients in which ADA could be detected in the PIA after 28 weeks of treatment were more prone to have low adalimumab levels (<5µg/ml) (p<0.01) and high ADA levels which could be detected in the antigen binding test (ABT) (p<0.05) at later time points. The PIA measurements also revealed transient ADA formation in 17/35 ADA producing patients.

Chapter 5 describes a study in which we investigated the mechanism by which ADA
formation leads to clinical non-response. Here we investigated the specificity of ADA in a cohort of 50 ADA producing RA patients. Inhibition experiments using patient derived anti-adalimumab monoclonal antibodies showed that a single antibody could compete with 98.65% (25th–75th percentiles: 98.25–99.90) of the ADA response in these patients. This shows that the immune response against adalimumab is highly restricted. In line with this restricted response we could detect small immune complexes in the circulation of patients. Further inhibition experiments using TNF showed that the restricted anti-adalimumab response is directed against the TNF binding region of adalimumab. This suggests that all ADA are able to neutralize adalimumab, thereby providing a mechanism by which ADA formation leads to clinical non-response.

We further investigated whether the restricted ADA response was the effect of outgrowth of a single B-cell clone or multiple B-cell clones. Therefore we produced a total of 16 human monoclonal antibodies against adalimumab derived from two different patients. In chapter 6 we show that all antibodies are from different combinations of V(D)J segments. Furthermore, we determined the affinity of 11 of these monoclonal antibodies and studied how the affinity influences their detection of ADA in different assays. We found that the influence of affinity is variable between different assays depending on the type of binding necessary for ADA detection.

In total the following picture emerges. Upon repeated adalimumab exposure part of the patients start to produce ADA. The antibody response is polyclonal and consists mainly of antibodies of IgG1 and IgG4 isotype. In the majority of ADA positive patients ADA are already produced within the first 28 weeks of treatment and in part of the patients antibody production is transient. All antibodies are directed against the idiotype of adalimumab and result in functional neutralization of the drug.