Pharmacokinetics and immunogenicity of TNF-inhibitors, towards optimised treatment of rheumatoid arthritis
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Summary
Topics addressed in this thesis are the clinical relevance of antidrug antibodies (ADA) and drug levels of tumour necrosis factor (TNF) inhibitors for response to therapy; the clinical relevance of detection methods of ADA; the possibility to adapt treatment strategies, not only based on clinical response but also on drug level test results, and the influence of concomitant medication on the immunogenicity of TNF-inhibitors. The key findings are listed in table 1.

Altogether, over the last years the emphasis has been shifted from immunogenicity to pharmacokinetics. For years, immunogenicity was the main subject to be studied. However, nowadays research should be focussed at pharmacokinetics, which can be influenced by multiple factors including immunogenicity and others, such as co-medication and patient and disease related factors.

In chapter 2 the effect of ADA on the long-term outcome of treatment with adalimumab in rheumatoid arthritis (RA) patients was investigated. During 3 years of follow-up, 28% of 272 patients developed ADA, detectable with the antigen binding test (ABT). Those ADA influenced the achievement of sustained minimal disease activity (DAS28 < 3.2) and remission (DAS28 < 2.6) and this was attributed to low drug levels in patients with ADA. An important new finding was the detection of ADA already after 4 weeks of treatment in approximately 10% of patients. This shed new light on the definitions of primary and secondary failure to treatment. In a subset of patients the adalimumab dose was increased. This induced disappearance of ADA detectable with the ABT in some patients, however, response was not restored.

Patients with detectable ADA during follow up, had at baseline a more longstanding and severe disease, indicated by longer disease duration and a higher percentage of patients with erosive disease. In addition, those patients less often used concomitant methotrexate and the dose of methotrexate was lower. Patients also had more active disease. This indicates that the state of the immune system, i.e. an active pro-inflammatory state, might influence the induction of an immune response to therapeutic antibodies.

Chapter 3 is a follow-up on a previously published novel method to detect ADA. In this chapter, 99 adalimumab treated RA patients were followed for 3 years. ADA were detected using a pH-shift-anti-idiotype ABT, which enabled the measurement of ADA in the presence of drug levels. Via an acid dissociation step, complexes of ADA and drug were dissociated. With this assay, it was shown that half of the patients developed ADA. Using the pH-shift-
anti-idiotype ABT, ADA can be detected at earlier time points and in a higher percentage of patients as compared to the regular ABT. However, these ADA were only clinically relevant if the amount of ADA formed exceeded the amount of drug present. In this case ADA are detectable with the ABT. These results highlight the importance of measuring drug levels. Transient ADA production was also observed in a proportion of patients, suggesting (potential) induction of tolerance. Due to the limited number of patients, the relatively short time period to study tolerance and the variable time needed for the immune system to overcome the immune response, presently no firm conclusions can be drawn regarding tolerance and its clinical relevance.

Chapter 4 showed the concentration-effect curve of adalimumab for RA patients at 6 months of treatment. Again it was shown that the absence of drug levels is related to a lack of clinical response. In patients with high drug levels (> 8 mg/l) there was no additional clinical benefit compared to patients with lower drug levels. The optimal adalimumab serum level ranges from 5 to 8 mg/l. These data suggest that a substantial part of the patients is treated with a dosage that is higher than necessary. More concentration-effect curves are needed for other drugs, time points and inflammatory diseases to support a more individualised treatment approach based on a combination of therapeutic drug monitoring and clinical response.

In chapter 5, a cost-effectiveness analysis of a personalised treatment approach was presented. The observed usual care in a cohort of adalimumab treated RA patients was compared to a simulated personalised algorithm in which treatment decisions were made after 6 months of therapy, based on clinical response and adalimumab serum levels. Treatment steps in this algorithm were based on observational studies and expert opinion. Analyses using a Markov model showed vast cost savings when the treatment strategy was according to the algorithm. Scenario analyses were all cost saving with gained effectiveness or limited loss of effectiveness of treatment. This study provides additional proof for a therapeutic drug monitoring based treatment approach. However, first consensus regarding the most appropriate algorithm should be reached and thereafter all treatment steps have to be validated in a randomised controlled trial.

Drug levels were investigated in a large cohort of etanercept-treated patients with RA in chapter 6. Patients with good response to treatment had the highest drug levels over 6
months time (3.4 – 3.8 mg/l), whereas drug levels for patient with moderate or non-response were lower (2.5 – 3.1 and 2.6 – 2.8 mg/l, respectively). When patients were stratified into quartiles according to the height of the etanercept level, most patients in the lowest quartile were non responders and most patients in the highest quartile were responders. Patients in the lowest quartile were more often female, had a higher body mass index and used lower doses of concomitant methotrexate. Clinical utility of drug level testing in etanercept is debatable since difference in drug levels between responders and non-responders were, although statistical significant, marginal.

In this study, no neutralising anti-etanercept antibodies were detected using four different assays. The inability to measure anti-etanercept antibodies does not imply that there are none, however, those antibodies might not be directed to the antigen binding side, but to the hinge region of the molecule, which is the only foreign part of the etanercept molecule. Whether those antibodies will be clinically relevant and to what extent remains speculative.

At the time of publication of the study described in chapter 7, no head-to-head comparisons of different TNF-inhibitors or other biologics were available. Therefore, the aim of this investigation was to compare the clinical outcome of adalimumab and etanercept in anti-TNF-naive RA patients in daily clinical practice. Overall etanercept and adalimumab appeared similar effective in achieving sustained clinical response during 3 years of follow-up. However, when the detection of ADA was taken into account, adalimumab-treated patients without an immunogenic reaction to the drug had the best clinical outcome, adalimumab-treated patients with ADA had the worst clinical outcome and etanercept-treated patients were in between. For example, 40% of ADA negative patients, 23% of etanercept-treated patients and 4% of ADA positive patients achieved at least sustained minimal disease activity. This implies that optimal response rates can be achieved in patients in which an immunogenic reaction can be prevented. In addition to co-administration of methotrexate, factors influencing an immunogenic reaction have to be identified.

Chapter 8a reviews the effect of concomitant methotrexate use on the immunogenicity of TNF-inhibitors (adalimumab and infliximab) in various inflammatory diseases. Results were mainly derived from observational studies. In patients concomitantly treated with either methotrexate or azathioprine the frequency of detectable ADA was lower than in patients on anti-TNF monotherapy.
Although knowledge of the effect of immunosuppressants on the immunogenicity of TNF-inhibitors is useful in clinical practice, a more practical question is what dose to use to obtain this effect. In chapter 8b it was shown that even low doses of methotrexate influence immunogenicity, however, the higher the dose (up to 25 mg per week) the larger the effect. This indicates that patients should be treated with the highest tolerated dose from the start of treatment, in this case with adalimumab, in order to minimise the immunogenicity of the drug.

The mechanism whereby methotrexate influences the immune response against TNF-inhibitors remains to be speculated. This could either be based on the suppression of the expansion of T- and B-cells or on the anti-inflammatory effect, leading to a lower TNF-load and higher drug concentrations, which are more difficult for the immune system to overcome. These findings might be even more important for inflammatory diseases in which co-administration of methotrexate is uncommon, for example ankylosing spondylitis or psoriasis.

Table 1. key findings of this thesis (ABT=antigen binding test; ADA=antidrug antibodies)

- ADA detected with an ABT impair long-term clinical outcome in patients with rheumatoid arthritis treated with adalimumab.
- With an ABT, ADA can already be detected after 4 weeks of treatment with adalimumab in a proportion of patients, shedding new light on the definitions of primary and secondary treatment failure.
- Patients with longstanding severe RA and active disease at baseline are more prone to develop ADA during follow-up. This might indicate that the state of the immune system, an active, pro-inflammatory state, might influence the induction of an immune response to biologicals.
- Using a Ph-shift-anti-idiotype ABT, ADA can be detected in approximately half of RA patients treated with adalimumab. However, ADA are only clinically relevant if the amount of ADA formed exceeds the amount of drug present. These ADA can be detected with a regular assay (e.g. ABT).
- Concentration-effect curves aid in the identification of a therapeutic window and could support a more individualised treatment approach, based on clinical response and pharmacokinetics.
- Analyses using a Markov model showed enormous cost savings when treatment was according to an algorithm combining clinical response and drug levels of adalimumab. These results provide additional evidence for a therapeutic drug monitoring based treatment approach.
- Etanercept treated RA patients responding well to treatment had higher drug levels than patients that did not respond to treatment. Several patient characteristics could identify patients with low etanercept serum levels.
- Overall, etanercept and adalimumab appeared similar effective in achieving sustained clinical response. However, most optimal response rates could be achieved in patients treated with adalimumab in which an immunogenic reaction to the drug could be prevented.
- Concomitant treatment with methotrexate lowers the frequency of ADA detected in observational studies. The effect of methotrexate on the immunogenicity of adalimumab proceeded in a dose-dependent manner.