Discussion:
Dose-to-target and research agenda
Treatment of rheumatoid arthritis (RA) is focused at treat-to-target, a strategy in which treatment adaptation is based on regular disease activity measurements, aiming at achieving remission of the disease.\(^1\) During the last decade biologics have prominently settled as a treatment option in RA and aid in achieving the treat-to-target goal. Approximately 10-30% of the RA population in rheumatology practise of western countries receive biologics.\(^2\) Despite large variation in pharmacokinetics and response to a certain dose, treatment with biologics is based on the principle of ‘one size fits all’, meaning that all patients are initially being treated with the same dose. As a result, there could be a substantial proportion of patients with over- or under treatment. Since costs of biologics, with sales of billions of dollars yearly, have become an urgent issue, health care insurances and governments all over the world try to restrict these costs.

Pharmacokinetics and dose of biologicals

Variation in pharmacokinetics is a consequence of a number of factors, which have been discussed in this thesis. Low or absent drug levels might be a result of an immunogenic reaction. Briefly, (neutralizing) antidrug antibodies (ADA) can bind to the idiotype of a therapeutic monoclonal antibody, thereby inhibiting the binding of the target.\(^3\) Whether this process is clinically relevant depends on the amount of ADA formed and thereby on the remaining free drug that can inhibit the target.\(^4\) In addition, pharmacokinetics is dependent on systemic inflammation and on co-medication, since these factors influence the amount of target present. These factors are listed in table 1. Furthermore, a proportion of patients with high drug levels can be identified where there seems to be no additional clinical benefit of high drug levels on disease activity, as can be concluded from a drug specific concentration-effect curve.\(^5\) However, the definition of high or low drug levels still needs consensus and might vary between inflammatory diseases or biologics. The construction of concentration-effect curves will give more insight in these definitions and aids in defining a therapeutic window.
Table 1. factors influencing pharmacokinetics of biologicals

- immunogenicity
- immunosuppressive co-medication
- drug specific characteristics, e.g.:
  - half-life
  - dose
  - administration route
- patients characteristics, e.g.:
  - gender
  - body mass index
- disease related factors, e.g.:
  - level of inflammation
  - severity of the disease

In addition to the variation in pharmacokinetics, there is a variation in the dose of a biologic needed to initiate a clinical response in individual patients. In general, to reach adequate response rates on group level, the registered dose of a biologic is a relative overtreatment in a substantial proportion of the patients. With this registered dose, safety issues remain within acceptable limits, however, costs are higher than necessary. This can be extrapolated from dose finding or registration trials of biologics: a significant number of patients achieve clinical response with dosages lower than the registered dose of the drug and these response rates are higher as compared to the placebo group. For example, in a trial of RA patients receiving adalimumab, 32 percent of the patients using 20 mg every two weeks reached an American College of Rheumatology 50% (ACR50) response. Corresponding response rate for patients on 40 mg every other week, the currently registered dose of adalimumab for RA, was 55 percent. For RA patients treated with tocilizumab, a therapeutic monoclonal antibody directed against the interleukin-6 receptor, ACR50 response for patients on 4mg/kg was 31 percent. Corresponding rate for patients receiving 8 mg/kg, the currently registered dose of tocilizumab, was 44 percent.

In addition, there is a variation in the dose of a biologic needed to maintain clinical response in individual patients and this dose is probably lower than the dose needed to initiate a clinical response. For example, in a randomised controlled trial of etanercept, patients with RA were assigned to the regular dose (50mg sc weekly), 25 mg weekly or placebo with background methotrexate after initial clinical response to etanercept regular dose. One year after dose reduction to 25 mg weekly, the proportion of patients that remained in minimal disease activity or remission was comparable to patients treated with the regular dose.

Since dose adaptations do not occur on a regular, standardised basis, there is a substantial proportion of patients with over- or under treatment. To deal with the financial toxicity of
over treatment with biologicals, research should be aimed at investigating ways adapt treatment in a controlled setting, herein drug level testing might play a role.

**Algorithms**

Various algorithms have been proposed to tailor treatment to individual patients based on the measurement of serum drug levels and ADA in addition to clinical response. These algorithms mainly comprise the use of TNF-inhibitors in RA and Crohn’s disease and focus mostly on lack or loss of response. Treatment strategies include shortening of the dose interval, dose escalation, dose de-escalation, switching to a second TNF-inhibitor, switching to a biological with another mechanism of action or discontinuation of biologic treatment.

Those algorithms agree on switching to another TNF-inhibitor in case of non response with absent drug levels due to ADA formation. Rationale for this step is based on observational studies, in which switching to a second TNF-inhibitor is more effective for patients who failed to response to their first TNF-inhibitor due to low or absent drug levels, compared with patients who failed to respond despite adequate drug levels. These findings also advocate switching to a biologic with another mechanism of action in case of non-response despite adequate drug levels. Since therapeutic alternatives vary between inflammatory diseases, switching to a biological with another mechanism of action is not (yet) an available option for all diseases, e.g. ankylosing spondylitis or Crohn’s disease.

The role of dose increase or shortening of dose interval in RA has mainly been studied with infliximab and drug levels were not taken into account. After dose escalation of adalimumab, we observed that ADA titres decreased without restoring clinical response. In contrast, in patients with Crohn’s disease without ADA but with low drug levels, dose increase resulted in recovery of clinical response and median survival time was comparable to patients with adequate drug levels without the need for dose increase. Therefore, in Crohn’s disease, algorithms comprise dose increase or shortening of dosing interval in patients with inadequate response, low drug levels and low or absent titres of ADA.

Costs of biologics hinder dose escalation in patients with RA. Moreover, this will only be useful in patients with absent or low ADA levels. For patients with other inflammatory diseases, such as ankylosing spondylitis or Crohn’s disease, biological therapeutic options are, at least in Europe, limited to TNF-inhibitors. Therefore, higher costs of therapy, related to increased dosing, will be better accepted or even necessary.
Some argue to measure drug levels (and ADA) in responding patients to determine the reason for response: despite inadequate drug levels or due to adequate drug levels. In this first group of patients, discontinuation of expensive drugs could be considered as an option, because it is questionable whether low disease activity can still be attributed to the drug. Development of concentration-effect curves could aid in rationally decreasing the dose of biologicals in patients with adequate response to a drug. Moreover, drug levels, in most cases, will probably not aid in the decision to discontinue a biologic, since if a patient is able to discontinue the drug, then the drug probably is not needed, irrespective the height of the drug level.

**Dose-to-target**

Combining the treat-to-target strategy with a dose-to-target strategy, in other words aiming at achieving maximal clinical effect with the lowest possible dose of a biologic, will improve treatment of RA and other inflammatory diseases and simultaneously reduce the financial burden of biologics and will therefore lead to a more tailored and optimal use of these drugs. Therapeutic drug monitoring (TDM) based adaptation of a dose will aid in this optimal use.

**Characteristics of therapeutic drug monitoring**

The measurement of serum drug levels is common for drugs with a narrow therapeutic window, such as lithium, digoxin and gentamycin. With these drugs there is a tight balance between the effective drug level and the drug level that causes (severe) side effects. In addition, TDM is applied when there is a wide inter-individual variability in serum drug concentrations reached with a certain dose of a drug. Based on this variability, a concentration-effect relationship can be defined to determine the therapeutic window of a drug. Furthermore, assays for drug level testing have to be available, reliable and standardised. Last but not least, the measurement of drug levels should be cost-effective. Characteristics of TDM are listed in table 2.

Drug level testing of biologics using an enzyme linked immunosorbent assay (ELISA) is straightforward and costs are low, approximately 50 euros, especially in relation to the costs of the medication itself. Although drug levels of biologics vary widely between patients, side effects are mostly limited and therefore, monitoring drug levels of biologics is not incorporated in daily practice. However, since the costs of biologics are a subject of debate, TDM can be advocated as an important tool to correct over- as well as under treatment and to support the treat-to-target approach, aiming at efficient use of expensive medication and
to treat patients in a controlled setting. Whether this dose-to-target approach will be cost-effective needs to be investigated further.

TDM is not only discussed in rheumatology, but in all therapeutic areas of biologics. However, objectives might be different. For example, in oncology TDM could guide the minimisation of under treatment of anticancer therapies which could have severe consequences for patients. Furthermore, TDM could aid in diagnosing toxicity, monitoring dose reduction or individualising doses in high-risk patients.

Antipsychotics, of non-biologic origin, have a narrow therapeutic window and therefore in psychiatry, TDM consensus guidelines are available. These guidelines recommend TDM of antipsychotics for dose optimisation, when non-compliance is suspected, in case of unexpected side effects, when clinical response is lacking despite adequate dose, with co-administration of drugs that might influence pharmacokinetics of the antipsychotic or for specific patients groups like elderly or children and for relapse prevention.

Table 2. characteristics of Therapeutic Drug Monitoring of biologics and its availability in rheumatology practice

<table>
<thead>
<tr>
<th>characteristic</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>availability of standardised assays</td>
<td>yes</td>
</tr>
<tr>
<td>narrow therapeutic window</td>
<td>no</td>
</tr>
<tr>
<td>relationship between drug level and clinical response</td>
<td>yes</td>
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<tr>
<td>cost-effective</td>
<td>yes</td>
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Summary research agenda

Obstacles to overcome before TDM can be implemented in rheumatology daily practice include further assay standardisation, wider availability of the assays and consensus on time point(s) during treatment of trough sampling. The construction of concentration-effect curves for various diseases and biologics is needed for better understanding of the pharmacokinetics of biologics and to identify the therapeutic window and potential cut offs for dose adaptation. Pharmacokinetic-pharmacodynamic modelling will support the quantification of different sources of the inter-individual variability in response to treatment. Furthermore, randomised clinical trials to test TDM based treatment adjustment strategies would aid in evidence based and cost-effective treatment algorithms based on both clinical
response and pharmacokinetics of biologics. This research supports a dose-to-target treatment approach and leads to personalised tailored treatment in a controlled setting.
Reference list


