Practical recommendations for the use of therapeutic drug monitoring of biopharmaceuticals in inflammatory diseases

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Abstract: Biopharmaceuticals directed against tumor necrosis factor-alpha, integrins, interleukins, interferons and their receptors have become key agents for the management of inflammatory diseases in the fields of gastroenterology, rheumatology, dermatology and neurology. However, response to these treatments is far from optimal. Therapeutic failure has been attributed in part to inadequate serum concentrations of the drug and the formation of antidrug antibodies (ADA). Therapeutic drug monitoring (TDM) based on drug concentrations and ADA represents a pharmacologically sound tool for guiding dosage adjustments to optimize exposure. Although becoming standard practice in tertiary care centers, the widespread accessibility and recognition of TDM is hindered by several hurdles, including a lack of education of health care providers on TDM. In this paper, the Monitoring of monoclonal Antibodies Group in Europe (MAGE) provides an introduction on the fundamental principles of the concept of TDM, aiming to educate clinicians and assist them in the process of implementing TDM of anti-inflammatory biopharmaceuticals.

Keywords: therapeutic drug monitoring, biopharmaceuticals, trough concentration, immunogenicity, antidrug antibodies, inflammatory diseases

Setting the scene

The approval of interferon beta-1b in 1995 by the European Medicines Agency (EMA) marked the start of a new therapeutic era for inflammatory diseases. This biopharmaceutical structurally and functionally mimics the cytokine interferon beta and is registered for the treatment of patients with relapsing–remitting multiple sclerosis (MS). One year later, the US Food and Drug Administration (FDA) approved interferon beta-1a for the same indication. In 1998, FDA approved the marketing of infliximab, a chimeric (sub-stem -xi-) monoclonal antibody targeting the pro-inflammatory cytokine tumor necrosis factor (TNF)-alpha, for the treatment of moderate-to-severe, active Crohn’s disease (CD) or fistulizing CD in patients who have not responded to conventional treatments such as a corticosteroid and/or an immunosuppressant. Also in 1998, etanercept, another TNF antagonist, was approved for reducing the signs and symptoms of active rheumatoid arthritis (RA) in patients with an unsatisfactory response to disease-modifying drugs. Unlike infliximab, etanercept was a fusion protein consisting of two identical chains of the recombinant human TNF receptor p75 monomer and the Fc domain of human IgG1. One year later, in 1999, the indication for infliximab was extended for the treatment of patients with RA. In 2002, yet another TNF antagonist was granted market authorization by FDA for the treatment of RA, adalimumab, which is a fully

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DOI: http://dx.doi.org/10.2147/CPAA.S138414

Running head recto: TDM of anti-inflammatory biopharmaceuticals

Running head verso: Dreesen et al

Year: 2017

Article Designation: REVIEW

Journal name: Clinical Pharmacology: Advances and Applications

Clinical Pharmacology: Advances and Applications 2017:9 101–111

Clinical Pharmacology: Advances and Applications downloaded from https://www.dovepress.com/ by 54.70.40.11 on 11-Jun-2018

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human (sub-stem -mu-) antibody. It was only until 2004, with the approval of natalizumab for the treatment of relapsing MS, that a novel inflammatory marker was targeted. Natalizu

Table 1 Biopharmaceuticals approved for the treatment of inflammatory diseases and their target trough concentration (range) during maintenance therapy

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>IBD</th>
<th>RA</th>
<th>Spondyloarthritis</th>
<th>Psoriasis</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF antagonists</td>
<td>Infliximab</td>
<td>3.0–7.0 μg/mL&lt;sup&gt;10&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5.0–10.0 μg/mL&lt;sup&gt;11&lt;/sup&gt;</td>
<td>5.0–8.0 μg/mL&lt;sup&gt;9&lt;/sup&gt;</td>
<td>5.0–8.0 μg/mL&lt;sup&gt;12&lt;/sup&gt;</td>
<td>3.5–7.0 μg/mL&lt;sup&gt;8&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Golimumab&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;4.1 μg/mL&lt;sup&gt;13&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Certolizumab pegol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Etanercept&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Integrin antagonists</td>
<td>Natalizumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Vedolizumab</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Interleukin 17A antagonist</td>
<td>Secukinumab</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Interleukin 6 receptor antigen</td>
<td>Tocilizumab</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Interleukin 12/23 antagonist</td>
<td>Ustekinumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;5.0 μg/mL&lt;sup&gt;14&lt;/sup&gt;</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>CTLA-4 agonist</td>
<td>Abatacept&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CD20 antagonist</td>
<td>Rituximab</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Amentuzumab</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Interferon</td>
<td>Interferon beta-1a</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Interferon beta-1b</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>PEG interferon beta-1a</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
<td>–</td>
</tr>
</tbody>
</table>

Notes: *Market authorization for ulcerative colitis only. **Market authorization for Crohn's disease only by FDA. IgG1 Fc fusion protein. –, No target concentration (range) for performing TDM has been established yet. The presented thresholds should be interpreted with caution as they are highly dependent on the cohort in which established (eg, influence of disease type and disease activity), the assays used (eg, different calibrators) and the targeted outcome.

Abbreviations: CD20, cluster of differentiation 20; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; FDA, US Food and Drug Administration; IBD, inflammatory bowel disease; MS, multiple sclerosis; NA, not applicable; PEG, polyethylene glycol; RA, rheumatoid arthritis; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.
ustekinumab, secukinumab, alemtuzumab and abatacept, data supporting a role for TDM are still particularly scarce.20,22,24–31

**Why perform TDM of biopharmaceuticals?**

The main reason to perform TDM of biopharmaceuticals is to provide the clinician with an objective tool to guide the therapeutic procedure. Clinicians and laboratories need to be made aware of the large variability in drug kinetics between patients and even within a patient over time. A more than 10-fold interindividual variation in trough concentrations (ie, the serum or plasma concentration just before a next infusion) has been described.26,32–34 Furthermore, adequate drug trough concentrations have been linked to response (clinical response, biomarker response, endoscopic response, etc) in different inflammatory diseases.18–22 As the correlation between drug blood concentrations and outcome is stronger than between dose and outcome, measuring drug concentrations is an essential part of TDM, and allows optimization of the therapeutic dosage regimen and thereby improvement of the response. Besides its therapeutic benefit, TDM can also avoid unnecessary therapeutic interventions and subsequently reduce costs.12,13,35

**When to perform TDM?**

Different clinical scenarios for performing TDM are suggested in literature and essentially come down to performing testing for drug and ADA, linking the test results to dosage regimen adaptations to induce (ie, reactive TDM) and maintain (ie, proactive TDM) adequate drug exposure and thereby response (Table 2).36–38

Subtherapeutic concentrations in the early stages of therapy, possibly as a result of high disease activity and/or to the production of ADA, are often associated with loss of response in the first year of treatment.6,39,40 Hence, performing TDM during induction and early maintenance therapy is useful to alert the clinician about the risk of clinical failure.2,41,42 Moreover, TDM can be used to identify real primary nonresponders having an adequate exposure to the drug.

A single measurement may be insufficient for problem-solving. To gain insight into the pharmacokinetic (PK) evolution over time in each patient, it is helpful to measure consecutive trough concentrations (eg, over three or four administrations). This is because disease activity might influence the drug’s PKs, and therefore trough concentrations may differ within a patient over time.43–46 Measuring consecutive trough samples and interpreting the drug concentrations with regard to the evolution of the therapeutic response provide a patient-specific “reference” trough concentration that is associated with response. Some patients have a good response with lower levels than others and this is intrinsic to each individual. However, this concept of patient-specific targets conflicts with the widely used “one-size-fits-all” target trough concentration concept, but clinical evidence is currently lacking.

One should always be aware of the factors that (may) cause interindividual and inter-occasion variability in drug exposure such as the changes in the dosage regimen (dose...
and/or dosing interval), changes in absorption and volume of distribution (which cannot be taken into account as this information is not captured in the trough concentration) and changes in drug clearance (which is information that is captured in the trough concentration). Besides trough concentrations, intermediate concentrations might thus be helpful to gain better insight into (the variability of) the PK profile (especially for the subcutaneously administered drugs). However, evidence for intermediate sampling is limited.47

Along the treatment, we recommend to use clinical follow-up with measuring drug concentrations at every visit during induction phase,40,46,48 and then once every 3–6 months unless clinical signs of loss of response arise or the clinician decides to perform drug tapering in case of sustained remission.14,15,49,50 The (cost) effectiveness of this recommendation needs to be established.

### How to perform TDM of biopharmaceuticals?

We briefly discuss the main steps in the TDM process (Figure 1): 1) the blood sampling, 2) the measurement techniques, 3) the communication and interpretation of the results and 4) the clinical decision-making support. Only then, fully substantiated dosage regimen recommendations can be made.

### Blood sampling for TDM

To make drug blood concentration measurements of value, attention must be paid to 1) the timing of blood sampling, 2) the type of blood sample and 3) the storage and shipment conditions of the sample.

### Timing of blood sampling

Errors in the timing of sampling are one of the greatest causes of misinterpretation of the results. TDM based on drug blood concentrations obtained at unknown or inappropriate time points is useless. As TDM of biopharmaceuticals is currently based on trough concentrations, the blood sample should be drawn just before the start of the next administration of the drug. At this moment, there are not many data on the therapeutic value of intermediate and peak drug concentration measurements, although the usefulness of intermediate measurements has been suggested to guide dose increase in patients with ADA at the end of the infusion cycle.47

Obtaining trough concentrations of the self-administered biopharmaceuticals is challenging in a way that adequate planning of visits is required. Intermediate blood samples are often collected for these subcutaneously administered drugs, but no data are currently available on the association between intermediate drug concentrations and therapeutic outcomes.

### Blood sample collection and preparation

Laboratory measurements of biopharmaceutical concentrations are typically performed on serum, but EDTA, heparin or citrate plasma samples may also be used in these assays.51–54 Serum tubes with clot activator and gel separator are recommended.51,52 To avoid hemolysis, serum should be removed from the clot as soon as possible (within 4 hours).51,52 Depending on the analysis technique and the use of a robot, volumes up to 0.5 mL of serum/plasma are required.

### Storage and shipment of samples

If blood samples are to be analyzed within 1 week, they may be stored at room temperature.55 However, recommendations

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**Table 2** Generic TDM algorithm for biopharmaceutical therapies of patients with inflammatory diseases

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Decision support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Response</td>
</tr>
<tr>
<td>Drug concentration at trough</td>
<td>ADA concentration at trough</td>
</tr>
<tr>
<td>Above target (range)</td>
<td>NA</td>
</tr>
<tr>
<td>Within target (range)</td>
<td>NA</td>
</tr>
<tr>
<td>Below target (range)</td>
<td>Undetectable</td>
</tr>
<tr>
<td></td>
<td>Detectable</td>
</tr>
<tr>
<td>Undetectable</td>
<td>Undetectablec</td>
</tr>
<tr>
<td>Detectabled</td>
<td>Detectabled</td>
</tr>
</tbody>
</table>

**Notes:** TDM algorithms typically provide decision support based on the measurement of drug and ADA concentrations. aUse a drug-tolerant ADA assay. bThe clinical evidence for different decision support options may vary between drugs/indications. cSwitch within drug class or to another drug class. dUse a drug-sensitive ADA assay. Always check for patient compliance in case of self-administered biopharmaceuticals, especially when drug concentrations are below the target (range). Change in dosage regimen is under responsibility of the treating clinician and it is necessary to assess for clinical response and drug concentration thereafter.

**Abbreviations:** ADA, antidrug antibody; NA, not applicable; TDM, therapeutic drug monitoring.
are generally more stringent and may differ between leaflets provided with TDM assays. Specimens are expected to be stable for at least 1 year when stored at -20°C, but stability studies are lacking. Samples can be aliquoted to 20°C, but to be stable for at least 1 year when stored at -maceutical itself.60

in which the ADA are detected using the labeled biophar-

somatic differences.62,63 Only results obtained with the same

unknown, as long as there is free drug detected in sample.

of measuring complexed ADA in clinical routine remains

format but so far, as the therapeutic action of a biopharma-

protocol allows earlier detection of ADA using the ELISA

calibrator for quantifying ADA will eventually facilitate

assay can be compared. The implementation of a universal

Communication and interpretation of the results
Communication of the results
The role of drug assay laboratories is to measure the con-

centration of a therapeutic drug in a sample. Laboratories

might vary in the way they report the results. The unit is

usually μg/mL or mg/L. They, however, do not provide dosage

recommendations. As trough concentration-based dosing is

not always supported by the leaflet of biopharmaceuticals,

there is often no legal framework for dosing based on blood

measurements. Clinical decision-making based on the mea-

sured concentrations is performed by the specialist following

evidence from literature or his/her own clinical experience

with the patient.11,12 When the drug concentration is below

the detection or quantification limit, this limit should then

be reported. Furthermore, correct interpretation of the assay

result requires the reporting of relevant information such as

drug sensitivity of the assay that is used. Ideally, drug assay

laboratories participate in an external quality assurance pro-

gram. Nevertheless, reporting of the assay used is important

when comparing measurements from different assays.

Interpretation of the results
Appropriate clinical interpretation of the assay results

requires information on 1) the dosage regimen (administered

doses and time of dosing), 2) the time of blood sampling

and 3) assay characteristics (eg, drug sensitive/tolerant ADA

assay).
Clinical decision-making about patient treatment

Measuring drug concentrations may guide clinicians to adapt dosing. A therapeutic window that is associated with response is a prerequisite for TDM-based clinical decision-making. If the drug concentration is below the therapeutic range in a patient, dose increase, interval shortening or a combination may be considered. Besides treatment intensification, TDM also includes the possibility of giving insights for reducing the exposure when needed, by reestablishing the standard dosing interval and/or dose de-escalation.14,15,70–72 These interventions have been integrated in TDM algorithms, for example, the Trough concentration Adapted infliXImab Treatment (TAXIT) algorithm, which can be used for optimizing maintenance infliximab therapy in patients with IBD.13 TDM algorithms usually are decision trees/matrices that suggest an intervention based on drug and ADA concentrations (Table 2).73 In a “treat-to-target” setting, blood concentrations are not the target but a guidance to achieve relevant targets such as disease control, mucosal healing or reduction in articular damage.74 The clinician must decide whether to change the treatment strategy or not, taking into account the information given by TDM. However, therapeutic ranges have not been established for all biopharmaceuticals in all anti-inflammatory diseases and prospective trials comparing TDM-based dosing and clinically based dosing are warranted there. The most straightforward situation is when the drug is not measurable. After excluding sampling errors, this can be explained in two ways. First, there can be an “overconsumption” of the drug by the high inflammatory burden or increased metabolization/excretion.44 This necessitates a treatment intensification. Second, there can be the formation of ADA. In this situation, treatment intensification is less successful.75 Moreover, treatment intensification in this setting may lead to severe allergic reactions, certainly when ADA concentrations are high.6,76 When ADA concentrations are low, an attempt may be performed to overcome the ADA.77 However, this must be performed with precaution and under anti-allergic prophylaxis.

Besides ADA, there are more factors that influence the effect of a treatment intensification on the drug exposure. Typically, body composition measures (eg, sex and body weight) and disease activity measures (eg, antigenic target load, C-reactive protein and albumin) are shown to affect the PKs of biopharmaceuticals and should be taken into account for individualized TDM.43–45,78–82 Clinical evidence for pharmacometric-driven TDM algorithms that take into account these patient-specific and time-varying factors is currently lacking, but great potential is expected (eg, ClinicalTrials.gov Identifiers: NCT02453776 and NCT02624037).

As mentioned earlier, TDM-based adaptation of the dosage regimen is typically not supported by the leaflet of biopharmaceuticals and, accordingly, the drug formulations and the reimbursement regulations do typically not allow much flexibility in drug dosage regimen. While fine adjustments of the dose are difficult, especially for subcutaneously administered drugs, it is more convenient to change the dosing interval.

Current status of TDM in inflammatory diseases

IBD

For the oldest biopharmaceuticals on the market, infliximab and adalimumab, the added value of TDM has been demonstrated repeatedly, while evidence for TDM of the more recently marketed golimumab, vedolizumab and ustekinumab is still limited.21 Especially in the context of reactive TDM, clinical decision-making algorithms based on infliximab/adalimumab and ADA measurements have been established.75,77,83–86 The role for proactive TDM of infliximab has been explored in the landmark studies, TAXIT and TAILORIX, but superiority over symptom-based dose optimization could not be demonstrated.12,87 Nevertheless, the TAXIT study shows that targeting patients within the 3–7 μg/mL trough concentration range results in an improved response in patients with CD (due to dose escalations) at a 28% lower drug cost (due to dose de-escalations).

RA

An exposure–response relation has been confirmed for all TNF antagonists that are approved for the treatment of patients with RA.88–92 More recently, an exposure–response relation has been reported for tocilizumab as well.93 For rituximab and abatacept, data are lacking.18 The impact of ADA on exposure and response has been reported for infliximab, adalimumab and golimumab.49,90,94 ADA toward certolizumab pegol were associated with lower drug concentration but not with a lower clinical response.92 Furthermore, ADA have been detected toward etanercept (although non-neutralizing antibodies), rituximab, tocilizumab and abatacept, but no impact on drug exposure and response has been observed.18,31,91,95,96 TDM-based treatment optimization of infliximab, adalimumab and etanercept has been explored in a few studies, overall suggesting a
cost-effectiveness. The utility of TDM of rituximab, tocilizumab and abatacept remains unclear.

Spondyloarthritis
Positive exposure–response correlations have been described for infliximab, adalimumab and etanercept, although not all studies could confirm this correlation. The discrepancies may be explained by differences in disease pathophysiology (eg, TNF-driven and non-TNF-driven disease) and by heterogeneity in the quantification of exposure (eg, different sampling times and different assays) and response (eg, different clinical disease scores). Furthermore, the clinical response to infliximab, but not to adalimumab, was higher in ADA-negative patients than in ADA-positive patients.

To date, no TDM algorithms have been assessed for biopharmaceutical therapies in spondyloarthritis.

Psoriasis
For infliximab and adalimumab, the immunogenicity–exposure–response correlation has repeatedly been described and therapeutic trough concentration thresholds have been suggested. Etanercept, on the other hand, is less immunogenic and trough concentrations vary less.

For the more recently marketed drugs, ustekinumab, secukinumab and ixekizumab, data supporting a role for TDM are still scarce but are expected in the foreseeable future.

MS
Currently available data support a role for TDM of natalizumab in the treatment of MS, as low natalizumab concentrations and high ADA are associated with a lack of therapeutic efficacy. On the contrary, studies exploring the exposure–response relation for interferon beta-1a and alemtuzumab are lacking. Nevertheless, neutralizing ADA against interferon beta-1a (ie, ADA that inhibit the binding between interferon beta-1a and interferon receptor) are shown to abolish the biological activity and subsequently the therapeutic efficacy. Therefore, TDM guidelines are in place which recommend a therapeutic strategy based on the measurement of neutralizing ADA and of the biological activity of interferon beta. This is, however, not the case for alemtuzumab, as one study by Cohen et al concluded that the presence and concentration of ADA against alemtuzumab did not influence lymphocyte depletion and repopulation, efficacy and safety.

Aims and position
In this paper, we provide an overview of the TDM process of biopharmaceuticals that are used to treat patients with inflammatory diseases. With the Monitoring of monoclonal Antibodies Group in Europe (MAGE), we aim to educate health care practitioners and thereby hoping to promote the implementation and optimal use of TDM of these anti-inflammatory biopharmaceuticals. The monitoring of anti-inflammatory biopharmaceuticals is of increasing interest for optimizing treatment as therapeutic nonresponse is often reflected in insufficient drug concentrations. TDM is a valuable tool for (cost-effective) treatment optimization of biopharmaceuticals and is to be considered as a clinical decision-support tool in combination with follow-up of clinical performance.

Acknowledgment
This review was funded by Le Studium Loire Valley Institute for Advanced Studies.

Disclosure
PB has served as a speaker for AbbVie and Takeda and as a consultant for Merck Sharp & Dohme (MSD), Janssen Biologicals, Hospira, Mundipharma, Roche, Takeda and AbbVie. DM participated on behalf of his institution in clinical trials sponsored by Abbvie, Roche, Bristol-Myers Squibb, Pfizer, Union Chimique Belge and MSD; his hospital received a grant for research from Abbvie in 2004 and from Nordic Pharma in 2012; he has acted as a consultant and given lectures on behalf of his institution for MSD, Novartis, Union Chimique Belge and Pfizer; and he has been invited to attend international congresses by MSD, Roche, BMS, AbbVie and Janssen-Cilag. AG has served as a speaker for MSD, Janssen Biologicals, Pfizer and AbbVie, as a consultant for Union Chimique Belge and has received investigator-initiated research grants from Pfizer. KU Leuven licensed the infliximab ELISA to apDia and R-Biopharm AG and the use of monoclonal antibody mAb-IFX6B7 in the lateral flow assay to R-Biopharm AG. KU Leuven licensed the anti-infliximab and adalimumab ELISA to apDia. DPS has served as a speaker for MSD, Pfizer, Novartis and AbbVie, as a consultant for AbbVie, Novartis and Takeda and has received research grants from Pfizer, Novartis and Progenika. ED reports no conflicts of interest in this work.

References


