Therapeutic Drug Monitoring of Monoclonal Antibodies in Inflammatory and Malignant Disease: Translating TNF-α Experience to Oncology

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Lack of response to monoclonal antibodies (mAbs) has been associated with inadequate mAb serum concentrations. Therapeutic drug monitoring (TDM) of mAbs has the potential to guide to more effective dosing in individual patients. This review discusses the mechanisms responsible for interpatient variability of mAb pharmacokinetics, summarizes exposure-response data of mAbs used in inflammatory and malignant disease, presents current evidence of mAb-TDM in inflammatory disease, and provides hurdles and required future steps for further implementing mAb-TDM.

Monoclonal antibodies (mAbs) are a class of drugs that have ameliorated the treatment of numerous diseases over the last decades. Parallel to the technical advances in the production of mAbs, the rapidly expanding biomolecular understanding of disease has identified numerous molecular targets for pharmacotherapeutic intervention. Together, this has led to the clinical development and introduction of numerous mAbs in the era of targeted medicine. The two major therapeutic classes of mAbs are the antiinflammatory mAbs for treatment of autoimmune diseases like rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), and the antitumor mAbs for the treatment of various solid tumors and hematological malignancies (**Table 1**).[1,2] Although mAb therapy has shown clinical benefit in many patients, initial response rates vary between 50–90% and in a majority of patients an initial response is lost over time, resulting in disease progression. Lack or loss of response to mAb treatment can be caused by many poorly understood epigenetic, biomolecular, or pathophysiological mechanisms,[3,4] whereas an inadequate mAb serum concentration is probably the simplest reason, although not yet widely acknowledged and studied.[5] Both for antiinflammatory mAbs and antitumor mAbs, therapeutic drug monitoring (TDM)-guided dose optimization based on measuring mAb serum concentrations in individual patients could therefore be the next dimension in personalized targeted mAb therapy.

PHARMACOKINETIC PRINCIPLES AND INTERPATIENT VARIABILITY OF mAbs

mAbs are 150-kD glycoproteins based on the structure of physiological γ-immunoglobulins (IgG) as produced by B-cells in response to exposure to antigens.[6] Progress in the development of therapeutic mAbs has resulted in pharmacokinetic properties of the latest generations of humanized and fully human mAbs similar to endogenous IgG; a volume of distribution approximating the circulating plasma volume and a half-life of 3–4 weeks.[7,8] Essential for the long half-life and low clearance rate of mAbs is the rescue from lysosomal degradation by binding to the neonatal Fc receptor (FcRn) in endothelial cells. Weak binding to the human FcRn of the first generations of murine and chimeric mAbs, together with their cross-species immunogenicity, resulted in short half-lives. Successor generations of humanized and fully human mAbs have improved human FcRn affinity and reduced immunogenicity with subsequently longer half-lives.[6–8]

In the development of mAbs, the traditional focus has been on improving target affinity and clinical activity, whereas interpretation of mAb pharmacokinetics was impeded by an incomplete understanding of the pharmacokinetic modeling principles of this unique class of drugs. This is exemplified by the development of the human epidermal growth factor receptor-2 (HER2) targeting mAb trastuzumab. When trastuzumab was introduced for metastatic breast cancer in 1998, the half-life was reported to be 5.8 days and trastuzumab was dosed weekly. Several years later, new pharmacokinetic

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Table 1 Overview of FDA and EMA approved mAbs used in inflammatory and malignant diseases

	Year of introduction	mAb type	Target	Approved indications
Antiinflammatory mAbs				
Infliximab	1998	Chimeric IgG1	TNF-α	CD, UC, RA, SA, PsA, PP
Adalimumab	2002	Human IgG	TNF-α	RA, SA, CD, UC, PsA, PP
Ustekinumab	2009	Human IgG1κ	IL12, IL13	PP, PsA
Golimumab	2009	Human IgG1κ	TNF-α	RA, PsA, SA, UC
Tocilizumab	2010	Humanized IgG1	IL6R	RA, sJIA
Vedolizumab	2014	Humanized IgG1	α4β7	UC, CD
Secokinumab	2015	Human IgG1	IL17A	PP
Antitumor mAbs				
Rituximab	1997	Chimeric IgG1	CD20	NHL, CLL, RA, WD
Trastuzumab	1998	Humanized IgG1	HER2	BC, GC
Alemtuzumab	2001	Humanized IgG1	CD52	CLL
Bevacizumab	2004	Humanized IgG1	VEGF-A	CRC, BC, NSCLC
Cetuximab	2004	Chimeric IgG1	EGFR	CRC, HNC
Panitumumab	2006	Human IgG2	EGFR	CRC
Ofatumumab	2009	Human IgG1	CD20	CLL
Ipilimumab	2011	Human IgG1κ	CTLA-4	Melanoma
Brentuximab vedotin	2011	Chimeric IgG1 ADC	CD30	HL, sALCL
Pertuzumab	2012	Humanized IgG1	HER2	BC
Trastuzumab-emtansine	2013	Humanized IgG1 ADC	HER2	BC
Obinutuzumab	2014	Humanized IgG1	CD20	CLL
Ramucirumab	2014	Human IgG1	VEGFR2	GC
Pembrolizumab	2014	Humanized IgG4	PD-1	Melanoma
Nivolumab	2014	Human IgG4	PD-1	Melanoma, NSCLC

RA, rheumatoid arthritis; PsA, psoriatic arthritis; PP, plaque psoriasis; SA, spondylitis ankylopoetica; UC, ulcerative colitis; sJIA, systemic juvenile idiopathic arthritis; CD, Crohns disease; BC, breast cancer; GC, gastric cancer; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; RCC, renal cell cancer; OC, ovarian cancer; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; WD, Wegener's disease; HNC, head and neck cancer; ADC, antibody drug conjugate; HL; Hodgkin's lymphoma; sALCL, systemic anaplastic large-cell lymphoma.

analyses and population pharmacokinetic modeling revealed the half-life to be 28.5 days based on a two-compartment model, allowing dosing with a 3-weekly interval.[9] For most other intravenously administered mAbs, the two-compartment model now has been used for pharmacokinetic modeling. When mAbs are administered subcutaneously, a one-compartment model is usually used because of the slow absorption.[7]

Understanding of mAb biodistribution was expanded by positron emission tomography (PET) studies with radiolabeled mAbs. In patients with metastatic cancers, PET imaging studies with zirconium-89 (^{89}Zr)-labeled trastuzumab and the vascular endothelial growth factor (VEGF) targeting mAb bevacizumab illustrated that these mAbs are cleared gradually from the circulation by liver, spleen, and kidneys and that they specifically accumulate at the target site. Additionally, PET studies provided evidence that mAbs are able to reach target sites within the human brain. Furthermore, the interpatient variability in mAb distribution and especially heterogeneity in accumulation at the target site were notable.[10,11]

Significant interpatient variability has also been reported in most pharmacokinetic studies of mAbs.[7,8] For trastuzumab, the interpatient variability in clearance and distribution volume is 43 and 29%, respectively.[9] For the tumor necrosis factor-α (TNF-α)-neutralizing mAb infliximab, similar interpatient variability in clearance and distribution volume are found with 34% and 18%, respectively.[12] Especially the interpatient variability in clearance is of relevance since this highly affects the serum concentrations at the end of the dosing interval (trough concentration, C_{trough}, **Figure 1**). In patients with increased mAb clearance, trough concentrations can be below the minimum effective concentration, resulting in suboptimal disease control at the end of the dosing interval. Hence, understanding the mechanisms responsible for the interpatient variability in mAb pharmacokinetics, and appropriately accounting for this variability, is essential to achieve optimal clinical responses.

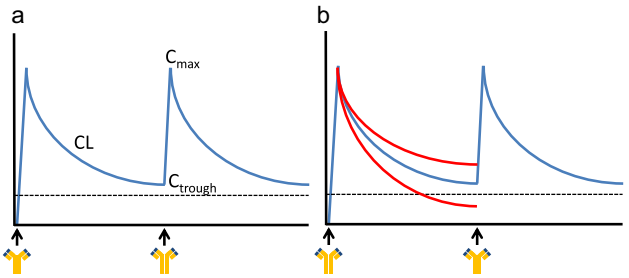

Figure 1 (**a**) Simplified pharmacokinetic presentation of the time–concentration curve of intravenous mAbs. The slow clearance (CL) of mAbs allows a dosing interval of one to more weeks for most mAbs. At the end of the dosing interval, the trough concentration (C_{trough}) should be above the minimum effective concentration (dashed line) for an optimal response. The maximum concentration (C_{max}) is reached directly after infusion. (**b**) The inter-patient variation in mAb clearance results in a wide range of trough concentrations (red lines). In a subset of patients, trough concentrations can be below the minimum effective concentration requiring dose intensification by either dose escalation or interval reduction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FACTORS INFLUENCING mAb PHARMACOKINETICS

Mechanisms responsible for the interpatient variability in mAb pharmacokinetics can involve demographic factors, disease factors, blood chemistry, immunogenicity, and treatment variables (**Figure 2**).

Demographic variables

Body weight and body surface area are the most frequent and clinically relevant covariates found in studies on mAb population pharmacokinetics.[8] Intuitively, the distribution volume is related to body size and most mAbs are dosed on body weight or body surface area to equalize mAb exposure between patients. However, since the circulating plasma volume is not linearly correlated with body weight, lean or obese patients might be under- or over-dosed, respectively, when the mAb dose is linearly corrected for body weight. Therefore, it has been suggested to use fixed-dosing to reduce the variability in exposure to mAbs with a limited effect of body size on their pharmacokinetics. In a suggested strategy for fixed-dose implementation in mAb drug development, the first-in-man study is started with fixed-dosing and during clinical development the decision to continue with fixed-dosing or body size-adjusted dosing is based on the therapeutic window, the effect of body size on pharmacokinetics, and whether or not this results in pharmacodynamic variability.[13,14] The HER2 targeting mAb pertuzumab is an example of successful implementation of fixed-dosing, although still 8.3% of patients are estimated to have trough concentrations below the target concentration of 20 mg/L.[15]

For some mAbs, gender is a covariate for clearance and distribution volume, even after correction for body size. Females have a clearance 23–39% slower and distribution volume 14–22% smaller compared to males in some studies with panitumumab, rituximab, bevacizumab, and infliximab. However, other studies did not find a body size-independent effect of gender on pharmacokinetics of rituximab or infliximab.[8] Although gender can be a significant covariate for mAb pharmacokinetics, the clinical relevance of this is unclear and gender-adjusted dosing currently is not recommended for any mAb.

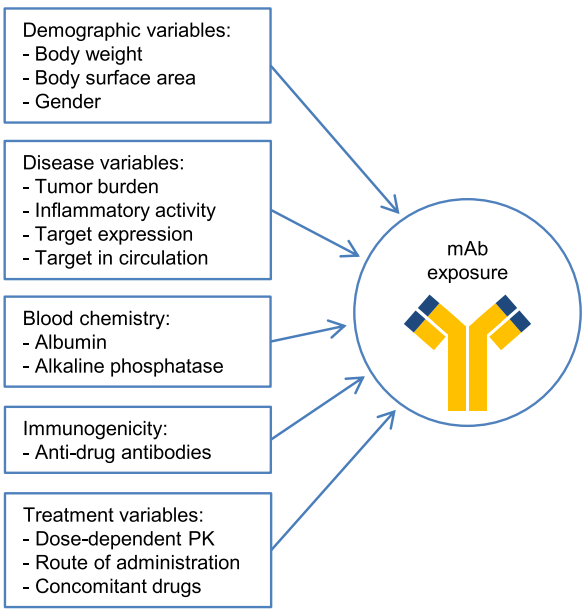

Figure 2 Schematic overview of covariates influencing mAb pharmacokinetics (PK) and thereby exposure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Disease variables

Both in inflammatory and malignant diseases, mAb targets can be present at the disease site as well as in the circulation. In principle, the fate of an mAb in the circulation is: 1) to enter the interstitial space at the disease site followed by target mediated degradation; 2) nonspecific clearance and subsequent degradation; or 3) specific binding to the target antigen in the circulation. When mAbs bind to their target antigen in the circulation, an antibody–antigen immune complex is formed that is prone to Fc_{γ}-receptor-mediated phagocytosis by immune cells.[16] Since antigen expression is directly related to disease activity, low mAb serum concentrations have been found in patients with the most active disease. In inflammatory disease this is illustrated by the finding that in patients with active IBD or RA, high levels of circulating TNF-α and C-reactive protein (CRP) are associated with increased clearance of infliximab.[17,18] In patients with HER2-positive metastatic breast cancer, high levels of circulating extracellular domain of HER2 result in increased clearance of trastuzumab.[9] For bevacizumab, a serum VEGF-dependent target-mediated drug disposition model has been described for colorectal cancer patients.[19]

The relation between TNF-α tissue burden, IBD disease severity, anti-TNF-α mAb tissue concentration, and anti-TNF-α mAb serum concentration was recently revealed in the ATLAS study. This study measured infliximab and adalimumab concentrations in tissue biopsies and found that mAb tissue concentrations correlated with serum concentrations of these anti-TNF-α mAbs, with a better correlation in patients in endoscopic remission. Tissue TNF-α levels correlated with the grade of mucosal inflammation and both TNF-α and anti-TNF-α mAb tissue concentrations were higher in inflamed tissue. However, the ratio of tissue TNF-α to anti-TNF-α mAb was elevated in tissue with

moderate to severe inflammation, suggesting that there is insufficient anti-TNF-α mAb to neutralize TNF-α in these tissues. Active IBD with high tissue levels of TNF-α thereby acts as a sink for anti-TNF-α mAbs.[20]

In malignant disease, a correlation between tumor burden and mAb pharmacokinetics has been described for several mAbs. In patients with HER2-positive metastatic breast cancer, the number of metastatic sites is the most impelling covariate for trastuzumab clearance, with a 22% higher clearance in patients with four or more metastatic sites. These are the patients mostly in need for effective trastuzumab levels, yet the increased clearance would result in a 18% lower exposure to trastuzumab at steady-state.[9] The tumor load-dependent pharmacokinetics of trastuzumab have also been demonstrated by ^{89}Zr-trastuzumab PET imaging in a patient with an extensive load of HER2-positive metastases. In this patient with an estimated tumor mass of 1.2 kg, it was calculated that the conventional loading dose of trastuzumab was unable to saturate the amount of HER2 target antigen in the tumor. On the ^{89}Zr-trastuzumab PET this was visualized by the prompt uptake of trastuzumab in the tumor and subsequent rapid clearance from the circulation.[21] Similarly, serum concentrations of rituximab, which targets CD20 on B-cells, are inversely correlated with the level of circulating B-cells in patients with B-cell lymphoma.[22] Furthermore, high tumor load is associated with low rituximab serum concentrations.[23] Interestingly, the second generation CD20 targeting mAbs ofatumumab and obinutuzumab also show similar target-dependent pharmacokinetics.[24,25]

Immunogenicity

As therapeutic mAbs are exogenous proteins, an immune response can develop during treatment with the formation of endogenous antiglobulins to the mAb.[7] The immunogenicity of mAbs is dependent on the structure and murine content of the mAb, immune status of a patient, concomitant use of immunosuppressive drugs, mAb dose regimen, and the route of administration.[8] When antibodies are formed against therapeutic mAbs, these antidrug antibodies (ADAs) are associated with increased mAb clearance and subsequently reduced mAb serum concentrations, and can result in loss of response. ADA formation in IBD patients with loss of response to adalimumab or infliximab is predictive for failure to dose intensification, while patients without ADAs respond well to dose intensification.[26] In a population pharmacokinetic study with infliximab in IBD, ADAs to infliximab were found in 31% of patients and ADA formation was associated with high infliximab clearance. Trough concentrations of infliximab were undetectable in 38% of the samples with ADAs to infliximab, whereas only 4.5% of the samples without ADAs to infliximab had undetectable troughs. Because of methodological reasons, ADA formation may have been underestimated in this study in the samples with detectable infliximab.[27]

Blood chemistry variables

Serum albumin and alkaline phosphatase levels have been identified as circulation covariates for mAb clearance. Bevacizumab clearance is 19% faster in patients with low serum albumin and 23% faster in patients with high alkaline phosphatase.[28] For pertuzumab clearance, serum albumin and alkaline phosphatase are, together with body weight, the most significant covariates.[15] Also with infliximab, a negative correlation has been found between serum albumin and infliximab clearance, with a 19.1% faster clearance in patients with low serum albumin.[29] The exact mechanisms by which low serum albumin and high alkaline phosphatase increase mAb clearance are not known, although it has been postulated that this reflects disease severity.[28] Another hypothesis is that low serum albumin levels are a result of FcRn impairment with associated faster immunoglobulin G (IgG) clearance.[8,29]

Treatment variables

Nonlinear dose-dependent pharmacokinetics have been described for several mAbs.[7,9,11] Rapid clearance from the circulation seen with low doses of the HER2 targeting mAbs trastuzumab and pertuzumab are probably the result of target binding which is not saturated at low mAb doses.[11] At therapeutic doses, mAb targets are generally saturated and mAb clearance is described by linear clearance. However, mAbs targeting soluble antigens with low endogenous levels like VEGF and TNF-α, also have dose-independent linear pharmacokinetics at low mAb doses.[30] In theory, very high mAb doses would saturate the FcRn with increased clearance rates as a consequence, although this has not been reported so far for any therapeutic mAb.[7] Saturation of FcRn is nevertheless possible with high doses of intravenous IgG (IVIG), and since it is unknown how this influences mAb clearance, measuring mAb serum concentrations should be considered when combining IVIG and mAb therapy.

Besides IVIG, other concomitant drugs can also influence mAb pharmacokinetics. The classic metabolic drug–drug interaction mechanisms as seen with small molecule drugs are generally not expected and examined with mAbs. However, mAb pharmacokinetics do have some typical mechanisms by which other drugs can interfere. As already explained, an immune reaction with the formation of ADAs results in increased clearance and reduced serum concentrations of mAbs. Many patients treated with antiinflammatory or antitumor mAbs are cotreated with immunosuppressive or cytostatic drugs, respectively. Since both immunosuppressive and cytostatic drugs interfere with immune reactions, these drugs can inhibit ADA formation, allowing for higher mAb serum concentrations. Furthermore, immunosuppressive drugs reduce TNF-α levels and inflammation, thereby potentially limiting the disease and target-mediated clearance of antiinflammatory mAbs. Conceivably by these mechanisms, methotrexate reduces clearance of infliximab and adalimumab.[31,32]

Antiinflammatory and antitumor mAbs are injected intravenously or subcutaneously and the difference in administration route influences mAb pharmacokinetics. Where intravenously injected mAbs have a bioavailability of 100% by definition; the bioavailability of subcutaneously mAbs is intermediate to high at 50–80%. Absorption of subcutaneous mAbs is facilitated by convection through lymphatic vessels during which a part of the mAb dose undergoes proteolytic degradation, explaining the reduced bioavailability. Because absorption by convection through lymphatic vessels is a slow process, peak serum concentrations (C_{max}) are reached in a few days (T_{max}) after

Table 2 Therapeutic drug monitoring rationale for mAbs used in inflammatory diseases and oncology

Drug characteristic requiring TDM	Antiinflammatory mAbs	Antitumor mAbs
Exposure-response relation	+	+
No direct clinical measurement of drug effect	+	+
Variation in pharmacokinetics	+	+
Small therapeutic window	+/−	+/−
Flexibility in dosing	+	+
Availability of a standardized and validated test	+/−	−

subcutaneous injection.[7,23] In an exemplary head-to-head comparison study, patients with HER2-positive early stage breast cancer were randomized between intravenous or subcutaneous trastuzumab. The mean T_{max} of the subcutaneous dose was 4.12 days, the mean C_{max} was higher in the intravenous group, mean C_{trough} was higher in the subcutaneous group, and other pharmacokinetic parameters were comparable for both administration routes. Interestingly, variation coefficients were slightly higher for C_{trough} and area under the curve (AUC) in the subcutaneous group, which can be a result of variability in subcutaneous absorption. The pharmacokinetic variation in the subcutaneous group increased the percentage of patients not reaching the target concentration of 20 mg/L from 1.3 to 3.0%, compared to the intravenous group.[33] Although this percentage is low, it has to be recognized that this is an observation in the neoadjuvant setting with early-stage breast cancer patients. The percentage of patients not reaching target trough concentrations can be higher when subcutaneous trastuzumab is used in patients with metastatic breast cancer because of the additional source of pharmacokinetic variation. Ongoing trials with subcutaneous trastuzumab in patients with advanced or metastatic breast cancer will have to elaborate on this issue.

In summary, there are many known covariates that influence mAb pharmacokinetics. Theoretically, one could calculate an optimal dose and interval for each individual patient based on body size, gender, disease activity/burden, immunogenicity, blood chemistry, and concomitant drugs. However, this methodology has several practical limitations and still could result in unexpected low mAb concentrations as a result of unforeseen variability in mAb pharmacokinetics, which known patient factors do not explain. A more practical approach would be to start mAb treatment with a conventional population pharmacokinetic-based dose and interval, followed by dose optimization based on measuring mAb serum concentrations. Serum concentration-guided dose optimization thereby has the potential to adjust for all covariates for interpatient variability, both known and unknown.

THERAPEUTIC DRUG MONITORING PRINCIPLES

Adjustment of drug dosing in individual patients based on serum concentrations to achieve maximal clinical efficacy and minimize adverse effects is referred to as therapeutic drug monitoring (TDM). TDM is routinely applied with selected antibiotics, antiepileptics, immunosuppressives, neuroleptics, and antiretroviral drugs. The rationale for TDM is not universally applicable for all types of drugs and requires one or more of the following characteristics of a drug: 1) correlation between serum concentration and response; 2) no direct clinical measurement of drug effect or toxicity; 3) interpatient variation in pharmacokinetics; 4) small therapeutic window; 5) flexibility in dosing; and 6) availability of a standardized and validated test for measurement of serum concentrations. Furthermore, a drug will not benefit from TDM when there is high within-subject variability. In general, mAbs have considerable interpatient variation in pharmacokinetics, limited directly measurable effects, and flexibility in dosing (**Table 2**). For mAbs there is no classic small therapeutic window with effective and toxic concentrations close together since most mAbs do not have a maximum tolerated dose. mAbs are costly drugs, however, and avoidable high serum concentrations could reduce unnecessary high expenses for mAbs. Most therapeutic mAbs are designed to continuously neutralize their target antigen and require a minimum concentration at which this is optimally achieved. TDM of mAbs consequently has the practical advantage that trough concentrations provide the most relevant information (**Figure 1**). Only one sample drawn at a convenient moment prior to the next dose could be sufficient for clinical decision guiding.[34] For implementation of TDM-guided clinical decision making, population pharmacokinetic studies have an essential role, as they provide an accurate analysis of the exposure–response relation, they quantify interpatient variability in pharmacokinetics, and they identify significant covariates. Studies on correlations between mAb serum concentration and efficacy are increasingly available for antiinflammatory mAbs (**Table 3**). However, data on exposure–response relationships for antitumor mAbs have been scarce until recently and this field of research is currently in its infancy.

mAb-TDM IN INFLAMMATORY DISEASE

Rheumatology

Studies on monitoring serum mAb concentrations in patients with RA or psoriatic arthritis (PsA) have thus far focused on adalimumab and infliximab. For exposure–response relationships in rheumatology, the Disease Activity Score of 28 joints (DAS28) is generally used. In 103 PsA patients, an exposure–response relationship has been reported for adalimumab with an optimal trough concentration range of 5–8 mg/L. Higher adalimumab concentrations did not result in improved DAS28 scores.[35] A similar exposure–response relationship was found for adalimumab in 221 RA patients, also with an optimal trough concentration range of 5–8 mg/L and no further DAS28 improvement in patients with trough concentrations above 8 mg/L.[36] In both adalimumab exposure–response studies, higher adalimumab trough concentrations were found in patients with concomitant use of methotrexate and lower concentrations were found in patients with ADAs to adalimumab.[35,36] Adalimumab ADA formation has been associated with reduced efficacy of adalimumab in RA patients indicated by higher DAS28 score, less patients achieving minimal disease activity or sustained remission, and

Table 3 Exposure-response relationships of mAbs used in inflammatory diseases and oncology

	Cutoff trough (mg/L)	*N*	Disease	Response endpoint	Ref.
Rheumatology					
Adalimumab	5–8	103	PsA	DAS28	35
	5–8	221	RA	DAS28	36
Infliximab	Various	428	RA	ACR response	43
	1.037	28	RA	Disease activity	44
	2.5	57	RA	EULAR response	45
Inflammatory bowel disease					
Adalimumab	0.33	120	CD	Sustained clinical response	49
	4.9	82	CD, UC	Clinical remission	48
	5.05–8.10	275	CD	Clinical remission	49
	4.5	142	CD, UC	Treatment failure	26
Infliximab	3.8	188	CD, UC	Treatment failure	26
	Time-dependent	728	UC	Clinical response, mucosal healing	51
	1.4	105	CD	Clinical remission rate	16
	1.4	115	UC	Clinical remission rate	52
	2.79	483	CD	Clinical remission	53
	3	327	CD	Symptomatic disease, inflammatory activity	54
	3	84	CD	Sustained response	55
	2.18	61	CD	Clinical remission	56
	6.26	46	UC	Clinical remission	56
	0.5	85	CD	Loss of response	57
	0.8	21	UC	Loss of response	57
	2	52	CD, UC	Clinical remission	59
Oncology					
Alemtuzumab	13.2	48	CLL	Complete or partial response	63
	6	29	CLL	Duration of response	65
Obinutuzumab	Various	285	CLL	Best overall response, progression-free survival	25
Rituximab	5.9–25.4	166	Lymphoma	Response	22
	70	66	B-cell lymphoma	Progression-free survival	67
	43.0–59.7	12	B-cell lymphoma	Response	68
Cetuximab	Various	33	Solid tumors	Response	69
	40.5	96	CRC	Progression-free survival	70
Trastuzumab	11.8	266	GC	Overall survival	72
Trastuzumab-emtansine	1.29	334	BC	Overall survival, progression-free survival, ORR	73

PsA, psoriatic arthritis; RA, rheumatoid arthritis; CD, Crohns disease; UC, ulcerative colitis; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; GC, gastric cancer; BC, breast cancer; ORR, objective response rate.

more frequent treatment discontinuation in patients with ADAs.[37] Exposure–response data on adalimumab have been further studied using pharmacokinetic-pharmacodynamic modeling. This resulted in a model where higher target trough concentrations are required in patients with high baseline DAS28 scores; 5 mg/L would be sufficient for patients with a DAS28 of 4.55, while 12 mg/L would be required with a DAS28 of 6.45.[38] Simulations with pharmacokinetic modeling showed that an adalimumab trough concentration of 11 mg/L would result in a 50% DAS28 improvement for a typical RA patient.[39] Adalimumab trough concentrations >12 mg/L are found in one-third of RA patients and since these high concentrations do not further improve response, there is a rationale for dose reduction in these patients with subsequently reduced treatment costs. TDM-guided clinical decision making in RA patients after 6 months of adalimumab was calculated to be cost-effective.[40] In summary, adalimumab TDM in rheumatology is currently supported by prospective observational cohort studies that have suggested an optimal adalimumab trough concentration range of 5–8 mg/L. Future prospective studies will have to indicate that TDM-guided dose optimization to this target range results in improved treatment outcome.

Analogous to the data on adalimumab, also for infliximab a correlation has been shown between trough concentrations, ADA formation, and clinical response in 35 RA patients.[41] In a response-guided infliximab dose escalation study, there was a positive correlation between dose and clinical response even in the subset of RA patients with ADAs. This observation suggests that low infliximab concentrations are a more important cause of inadequate response than ADA formation.[42] Exposure–response analysis for infliximab in 428 RA patients treated with 3 mg/kg every 8 weeks showed that in 26% of the patients there are no detectable trough concentrations at week 54. Higher trough concentrations were associated with increased responses to infliximab and patients with low or undetectable trough concentrations could thus benefit from TDM-guided dose intensification. With pharmacokinetic modeling, it was shown that dose intensification by shortening the dosing interval from 8 to 6 weeks would raise infliximab trough concentrations more than increasing the dose.[43] Because low infliximab trough concentrations are associated with reduced response to infliximab, it is possible to use infliximab trough concentrations as a predictive marker for long-term disease control in RA. Trough concentrations >1.037 mg/L predicted low disease activity at week 42 with a 84% sensitivity, 78% specificity, and an area under the receiver operator characteristic (ROC) curve of 0.83.[44] Improved response prediction was possible when combining disease activity and infliximab trough concentration, allowing to indicate at an early stage during treatment the patients most likely not to benefit.[45] Patients with a predicted low response, however, are most likely to benefit from TDM-guided dose optimization. Using infliximab TDM and disease activity together for clinical decision making in the treatment of RA patients thereby becomes attractive. Using <2 mg/L as low, 2–8 mg/L as medium, and >8 mg/L as high infliximab trough concentration cutoffs, infliximab TDM altered the therapeutic decision in 50% of infliximab-treated RA patients. In the subset of patients in whom the infliximab dose had been increased based on TDM, the mean DAS28 decreased by 20% and DAS28 improvement was correlated with increased trough concentration of infliximab.[46] The findings from this small study, together with the exposure-response data on infliximab in rheumatology, encourages further investigation of TDM-guided infliximab dose optimization in rheumatology. The optimal target range concentration of infliximab in rheumatology needs to be evaluated in future studies.

Inflammatory bowel disease

Therapeutic drug monitoring of TNF-α neutralizing mAbs is increasingly incorporated in the management of patients with Crohn's disease (CD) or ulcerative colitis (UC) based on the emerging evidence to support this approach. As in rheumatology, most experience has been obtained with adalimumab and infliximab.

In 168 CD patients, adalimumab trough concentrations were studied in relation to short-term (≤12 weeks) and long-term (>12 weeks) clinical benefit. In this study, patients received dose intensification by interval reduction at loss of response, with a subsequent clinical response in 71.6% of patients. While there was no correlation between adalimumab trough concentrations and short-term clinical response, there was a strong correlation between an increase in trough concentration after dose intensification and clinical response to dose intensification. The average adalimumab trough concentration increased after dose intensification from 4.8 to 9.4 mg/L, with an increase of 5.9 mg/L for responders and 0.0 mg/L for nonresponders.[47] TDM-guided dose optimization of adalimumab at loss of response might therefore be of value in IBD. In a study with 82 IBD patients having a disease flare after a primary response to adalimumab, a cutoff trough concentration of 4.9 mg/L was strongly predictive for clinical remission after dose escalation.[48] Thus, TDM of adalimumab predicts response to dose intensification in patients with loss of response. Additionally, adalimumab TDM has also shown to be valuable early during treatment. In a retrospective analysis of adalimumab trough concentrations in 275 patients from two clinical trials, early remission at 4 weeks was associated with higher trough concentrations (8.10 mg/L in responders and 5.05 mg/L in nonresponders). However, no cutoff threshold was found to be able to identify responders at weeks 24 or 56.[49] A meta-analysis of five studies showed that by using a cutoff of 4.85–5.39 mg/L, CD patients with an adalimumab trough concentration above this cutoff were two times more likely to be in remission, with an odds ratio (OR) of 2.6 (95% confidence interval [CI]: 1.79–3.77, $P < 0.0001$). Furthermore, patients with ADA formation to adalimumab had an OR for loss of response to adalimumab of 10.15 (95% CI: 3.90–26.40, $P < 0.0001$).[50] Adequate adalimumab trough levels in IBD were recently described as >4.5 mg/L, since this cutoff was able to identify the patients who failed to respond to dose escalation or switch to another TNF-α mAb with 90% specificity.[26] When combining adalimumab exposure–response data from both rheumatology and IBD, it can be concluded that a trough concentration below ~5 mg/L is inadequate for most patients. The optimal target range of adalimumab in IBD to be used in future TDM studies still has to be evaluated. The adalimumab

exposure–response data, however, supports further investigation of adalimumab TDM in IBD.

Infliximab trough concentration measurement has been performed in many IBD patients, both in clinical trials and in the management of patients with lack or loss of response. The main challenge in the implementation of infliximab TDM in IBD is the wide range of cutoff trough concentrations that have been reported with different response endpoints (**Table 3**). In a study with 728 patients with moderate-to-severe UC, high infliximab trough concentrations at weeks 8, 30, and 54 were associated with clinical response, mucosal healing, and/or clinical remission. The difference in infliximab trough concentrations between responders and nonresponders increased from week 8 to week 30 and was highest at week 54. For clinical response at week 8 of induction therapy, a cutoff trough concentration at induction of 41 mg/L showed a sensitivity, specificity, and positive predictive value (PPV) of 63%, 62%, and 80%, respectively. For maintenance of a clinical response at week 30, a cutoff trough concentration of 3.7 mg/L during maintenance therapy had a sensitivity, specificity, and PPV of 65%, 71%, and 82%, respectively.[51] In another study with 105 CD patients on infliximab maintenance therapy, clinical outcome could be predicted by trough concentrations. Patients with infliximab trough concentrations >1.4 mg/L had a 82% clinical remission rate vs. 6% in patients with <1.4 mg/L.[16] Similar results were found in 115 patients with UC, with 69% clinical remission rate in patients with infliximab trough concentrations >1.4 mg/L, and 15% in patients with <1.4 mg/L.[52] In a database analysis from four studies with 483 CD patients, an infliximab trough concentration >2.79 mg/L was associated with remission (77.6% specificity and 52.5% sensitivity).[53] The relation between infliximab trough concentrations and disease activity was confirmed in a prospective study with 327 CD patients which showed that concentrations <3 mg/L were associated with symptomatic disease and inflammatory activity.[54] The same cutoff trough concentration of 3 mg/L at the start of infliximab maintenance in 84 CD patients was found to be predictive for sustained response.[55] An infliximab trough concentration >3.8 mg/L was defined as adequate in a study with 188 IBD patients, since this cutoff predicted patients who failed to respond to dose intensification with 90% specificity.[26] Another prospective study with CD and UC patients used ROC curve analysis to identify a cutoff infliximab trough concentration of 2.18 mg/L for patients with CD and 6.26 mg/L for UC.[56] Using a similar approach, also a much lower infliximab cutoff concentration of 0.5–0.8 mg/L has been calculated to best identify IBD patients with clinical response to infliximab.[57]

These studies on the exposure–response relation of infliximab in IBD support the further investigation of infliximab TDM in patients with IBD. Although there is a range of published infliximab trough cutoff concentrations for IBD patients, it is evident that low infliximab concentrations are associated with poor clinical responses. Patients with low infliximab trough concentrations therefore are likely to benefit from dose intensification, which can be either dose escalation or interval reduction. Dose intensification by interval reduction (5 mg/kg every 4 weeks) was studied in 42 CD patients with treatment failure to infliximab. In 21 patients (50%), a clinical response to infliximab was regained after dose intensification. All responders had an infliximab trough concentration increase of ≥2.6 mg/L and the response could be predicted with 100% sensitivity and 50% specificity. Interestingly, ADAs to infliximab measured before dose intensification were found to be nonfunctional and became undetectable after dose intensification.[58] In a prospective study with 52 IBD patients, dose intensification by dose escalation from 5 to 10 mg/kg was performed after secondary failure to infliximab. Clinical remission was achieved in 58% of patients at 8 weeks after infliximab intensification. Low infliximab trough concentration (<2 mg/L) before intensification and the increase in infliximab trough concentration after intensification were both correlated with clinical remission. Infliximab ADA concentrations were similar in responders and nonresponders.[59] These two studies indicate that infliximab TDM might be of value at loss of response during treatment of patients with IBD. In a pilot observational study, retrospective clinical course analysis of TDM-guided infliximab dose adjustments in 48 IBD patients was found to be superior to standard care in a control group in terms of treatment duration. With an infliximab trough target range of 5–10 mg/L, TDM-guided dose intensification was performed in 12 patients (25%) and dose reduction was performed in 7 patients (15%). Patients in the TDM group had a 86% chance of being on infliximab after 5 years vs. 52% in the control group (hazard ratio 0.3; $P = 0.0006$).[60] Although with the limitations of a retrospective observational study, these results support further exploration of infliximab TDM in IBD.

The first prospective randomized trial on infliximab TDM in IBD has recently been published as the TAXIT study. In this study, 263 patients (178 with CD and 85 with UC) with a stable response to infliximab maintenance therapy were optimized by dose escalation or reduction to reach an infliximab target trough concentration of 3–7 mg/L. Following dose optimization, patients were randomized to TDM-guided treatment continuation or clinical feature-guided treatment continuation with a follow-up of 1 year. At baseline, only 44.0% of the patients had the target trough concentration of 3–7 mg/L, with 29.8% patients <3 and 26.2% >7 mg/L. Of the patients with trough concentrations <3 mg/L, 91% achieved the target concentration after dose escalation. In CD patients but not in UC patients, this was associated with a higher percentage of patients in remission with an increase from 65 to 88% (OR 4.1; $P = 0.020$). Of the patients with trough concentrations >7 mg/L, 93% achieved the target concentration after dose reduction. There was no difference in remission rates between both randomization groups. However, disease relapse rate was higher in the clinical feature-guided group compared to the TDM-guided group, 17 and 7% ($P = 0.018$), respectively. This study showed that IBD patients benefit from TDM-guided infliximab dose optimization and continuous TDM guidance is not necessary during maintenance therapy when initial dose optimization has been performed. Additionally, TDM-guided dose reductions of infliximab were safe, with no increase in disease flare or inflammatory markers and led to significant cost savings.[61]

Overall, the rapidly expanding amount of clinical data obtained with TDM of infliximab and adalimumab in rheumatology and IBD shows: 1) a consistently strong exposure–response relation; 2) substantial percentages of patients not at

target trough concentration either requiring dose intensification or allowing dose reduction; 3) TDM predicts patients likely to benefit from dose intensification; 4) better disease control after TDM-guided dose optimization; and 5) TDM-guided dose optimization is safe, cost-effective, and possibly even cost-reducing.

mAb-TDM IN ONCOLOGY

Classic chemotherapeutics used in oncology are the utmost example of drugs with a narrow therapeutic window and the optimal balance between efficacy and toxicity is generally evaluated for each individual patient. Chemotherapeutics are generally dosed at the maximum-tolerated dose as assessed in phase I dose-escalation studies. Toxicity guided dose-reductions are common practice during treatment with chemotherapeutics and since TDM is of limited value in this setting, oncologists do not widely embrace TDM in the treatment of their patients. However, toxicity of many antitumor mAbs is not dose-dependent with subsequently no dose-limiting toxicity and thus no maximum-tolerated dose in dose-escalation studies. Finding the optimal dose in early clinical studies with antitumor mAbs is therefore challenging since this involves target saturation and response data rather than toxicity data. The current dosing approach in oncology for chemotherapeutics and especially targeted therapies including mAbs is known to be suboptimal for some patients and this requires improved dosing strategies to achieve an optimal drug exposure in each individual patient.[62] Individualized mAb dosing guided by TDM therefore has potential to be of value in oncology,[34] similar as it has shown to be of value in inflammatory disease as described in the previous section.

Hematological malignancies

In an alemtuzumab population pharmacokinetic-pharmacodynamic study in chronic lymphocytic leukemia (CLL) patients, outcome data were available for 48 patients allowing study of the exposure–response relationship. Alemtuzumab trough concentration was found to be a predictor of response, with a mean trough concentration of 5.2 mg/L in nonresponders and 10.2 mg/L in responders ($P = 0.0003$). A cutoff trough concentration of 13.2 mg/L was able to indicate patients with ≥50% chance of a complete or partial response.[63] In another study with 30 alemtuzumab-treated CLL patients, high alemtuzumab trough concentrations were similarly associated with a better clinical response and minimal residual disease ($P < 0.02$).[64] Further evidence of the exposure–response relationship of alemtuzumab was provided in 29 CLL patients treated with subcutaneous alemtuzumab. Higher alemtuzumab trough concentrations were found in responders compared to nonresponders: 9.3 mg/L vs. 0.1 mg/L ($P = 0.003$), respectively. In the responding patients with an end-of-treatment alemtuzumab concentration >6 mg/L, the duration of response was longer compared to responding patients with <6 mg/L; 21.2 vs. 8.9 months ($P = 0.05$), respectively.[65] The difference in alemtuzumab concentration between responders and nonresponders has not been fully explained yet, although low and undetectable alemtuzumab concentrations have previously been found in patients with high lymphocyte counts. Based on the strong exposure–response relationship for alemtuzumab, it has been proposed to use TDM-guided alemtuzumab dosing in CLL to ensure adequate serum concentrations in each individual patient.[66] Whether TDM-guided dose optimization can bridge the 100-fold concentration gap between responders and nonresponders, and how this will result in improved outcome, will both have to be evaluated in future prospective studies.

Similar to alemtuzumab, an exposure–response relationship of the CD20 targeting obinutuzumab was recently described in 285 CLL patients. High obinutuzumab exposure was associated with a greater percentage change in tumor size, greater best overall response, and prolonged progression-free survival. This exposure–response relationship was especially strong in patients with a high baseline tumor size. Interestingly, also the exposure–safety relationship was studied and this showed no association between obinutuzumab exposure and the occurrence of serious adverse events.[25] The lack of an exposure–safety relationship is beneficial for TDM-guided dose optimization in future studies since this will mitigate toxicity concerns for patients requiring dose intensification.

Rituximab is another CD20 targeting antibody used in hematological malignancies and rheumatology. In 166 patients with low-grade lymphoma, higher rituximab concentrations were measured in patients with a response.[22] The exposure–response relationship of rituximab has been further studied in 66 patients with indolent B-cell lymphoma or mantle cell lymphoma. Although there was no difference in rituximab trough concentrations between responders and nonresponders, there was a strong correlation ($P = 0.007$) between rituximab trough concentration and progression-free survival, with a cutoff concentration of 70 mg/L.[67] In an analysis of 12 rituximab-treated B-cell lymphoma patients, rituximab trough concentrations were higher in responders compared to nonresponders ($P = 0.021$).[68]

Solid tumors

In a phase I study of the epidermal growth factor receptor (EGFR) targeting cetuximab in 33 patients with epithelial malignancies, patients with a response had a higher cetuximab trough concentration compared to patients with progressive disease ($P = 0.002$).[69] In 96 patients with metastatic colorectal cancer treated with cetuximab at a standard dose regimen of 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly maintenance, trough concentrations after two doses were studied in relation to progression-free survival. Patients with a cetuximab trough concentration below the median value of 40.5 mg/L at day 14, had a median progression-free survival of 3.3 months vs. 7.8 months in patients with a concentration >40.5 mg/L ($P = 0.004$). Although described in other cetuximab trials, no correlation between skin toxicity and progression-free survival was found in this study.[70] The strong exposure–response relation warrants individualized dose optimization for cetuximab. In the first cetuximab dose optimization attempt, 89 patients with metastatic colorectal cancer and grade ≤1 skin reactions on day 21 were randomized between dose escalation up to 500 mg/m^2 or continue on 250 mg/m^2. Patients in the dose escalation group showed a tendency to improved objective response rate and disease control rate compared to standard dosing (30 and 70% vs. 16 and 58%, respectively), although significance was not reached.[71]

Trastuzumab has been used in many patients with HER2-positive breast cancer since its introduction in 1998 and since

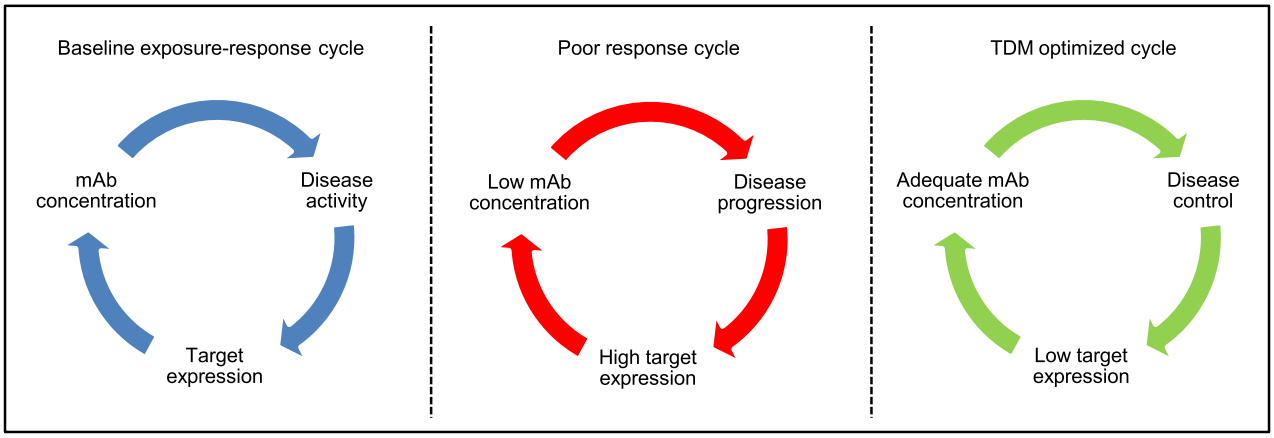

Figure 3 Exposure–response cycle of mAbs. An adequate mAb concentration results in disease control or remission, a subtherapeutic mAb concentration results in disease progression. Disease activity directly influences mAb target expression, both at the disease site and in the circulation. Target dependent clearance of mAbs results in low mAb concentrations in patients with active disease, while adequate concentrations can be maintained in patients with disease control. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2010 is also approved for treating patients with HER2-positive metastatic gastric cancer. Although the population pharmacokinetic model for trastuzumab in metastatic breast cancer predicted a below target trough concentration for 20% of the patients treated with a loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks,[9] the clinical relevance of this has not yet been studied. For patients with metastatic gastric cancer, the standard trastuzumab dose regimen is equal to the 3-weekly schedule for metastatic breast cancer. Translating the trastuzumab dose regimen from one indication to another, however, does not necessarily result in the most optimal regimen for all patients. In a combined case-control exposure–response analysis of the US Food and Drug Administration (FDA), the standard 3-weekly trastuzumab dose regimen was found to be suboptimal for a subgroup of patients. Based on the trastuzumab trough concentration at the end of cycle 1 (day 21), 266 patients were separated in quartiles. Patients in the lowest quartile with trastuzumab trough concentrations <11.8 mg/L had a median overall survival of 7.7 months, which was 8 months shorter than in the other quartiles and similar to the median overall survival of 7.5 months in the matched control group. Even after correction for negative prognostic factors, trastuzumab exposure remained predictive for overall survival. No relation was found between trastuzumab exposure and toxicity. The lack of survival benefit in patients with trastuzumab trough concentration <11.8 mg/L was considered a safety concern. Therefore, the FDA review team recommended performing a prospective trial to investigate whether a higher trastuzumab exposure can be achieved by dose intensification in patients with low trough concentration at the end of cycle 1 and how this would result in survival benefit.[72] A TDM-guided dose intensification study is of potential value in this setting.

The FDA also studied the exposure–response relationship of the antibody-drug conjugate trastuzumab-emtansine in patients with HER2-positive metastatic breast cancer. Patients (n = 334) were stratified into four quartiles based on end of cycle 1 (day 21) trastuzumab-emtansine trough concentration: Q1 ≤1.29 mg/L; Q2 1.29–1.99 mg/L; Q3 1.99–2.75 mg/L; and Q4 >2.75 mg/L. There was a strong correlation between trastuzumab-emtansine trough concentration quartile and median survival (16.1, 26.5, and 34.1 months in Q1, Q2, and Q3, while in Q4 median survival time was not reached). In addition, progression-free survival was related to trastuzumab-emtansine trough concentration quartile in similar manner (6.7, 6.9, 9.9, and 13.8 months in Q1, Q2, Q3, and Q4, respectively). Furthermore, there was an exposure–response relation for objective response rate. No relationship was found between trastuzumab-emtansine trough concentration quartiles and toxicity. Based on the evident exposure–response relation of trastuzumab-emtansine, TDM-guided dosing of trastuzumab-emtansine has been proposed as one of the strategies to improve exposure and thereby survival in patients with low trough concentrations.[73]

In summary, the exposure–response relationships currently described for alemtuzumab, obinutuzumab, rituximab, cetuximab, trastuzumab, and trastuzumab-emtansine provide encouraging evidence for further exploration of mAb-TDM in oncology. Although still in its infancy, mAb-TDM in oncology is likely to mature in the coming decade. During this process, experience from TDM development of anti-TNF-α mAbs can be translated to antitumor mAbs. For example, the ongoing discussion on the optimal target range of anti-TNF-α mAbs can be avoided by well-designed prospective studies evaluating the target concentration range of antitumor mAbs. The preferable outcome parameter in oncology is overall survival; however, also response rate and progression-free survival might be of value to validate the target concentration of antitumor mAbs in tumor types with relatively good outcomes. Where many TDM studies with anti-TNF-α mAbs were performed in patients having disease progression on a standard dose, this approach is obviously not suitable in oncology. Therefore, mAb-TDM in oncology should focus on TDM-guided dose optimization early during treatment. The TAXIT study with infliximab in IBD showed that after initial TDM-guided dose optimization, there is no benefit of continuous TDM and this might also be the case for antitumor mAbs. However, studies that do assess mAb serum

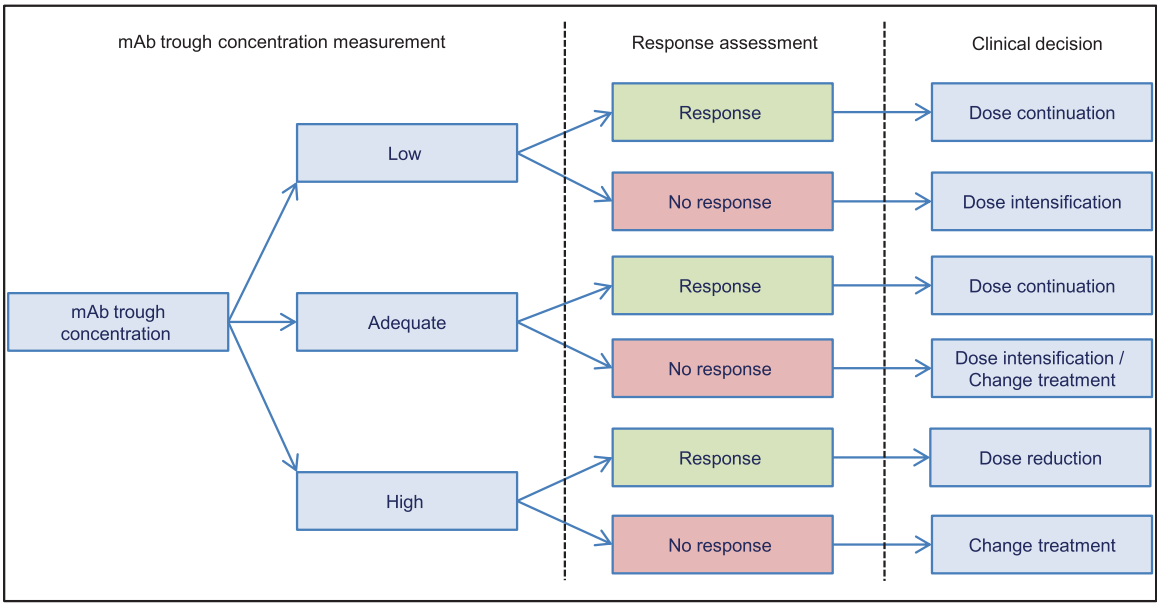

Figure 4 Generic treatment algorithm for therapeutic drug monitoring (TDM)-guided clinical decision making in mAb therapy. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

concentration at disease progression in patients that have been dose-optimized early during treatment will be informative on possible changes in mAb concentration at treatment failure. Furthermore, mAb-TDM studies in patients with stable inflammatory disease showed substantial percentages of patients with unnecessarily high mAb concentrations, allowing for TDM-guided dose reductions. In oncology this option has to be carefully assessed and possibly will differ for the adjuvant or metastatic setting.

EXPOSURE–RESPONSE CYCLE OF mAbs

Both for anti-TNF-α and antitumor mAbs, there is an increasing abundance of evidence for their exposure–response relationships. Combining exposure–response relationships with the target-dependent clearance of mAbs results in the concept of an exposure–response cycle with mAb concentration, disease activity, and target expression as interconnected variables (**Figure 3**). Patients with high disease activity, high target expression, and low mAb concentration are captured in a poor response cycle and are most in need of dose optimization. mAb concentration, disease activity, and target expression all can be measured; however, the mAb concentration is the only tunable variable in the exposure–response cycle. By individual tuning to an optimal target mAb concentration guided by TDM, the exposure–response cycle can be modulated in order to achieve maximum disease control.

HURDLES TO OVERCOME FOR ROUTINE IMPLEMENTATION

Despite the rapidly emerging evidence for mAb-TDM, there are still some major questions that first have to be answered before mAb-TDM will be widely advocated in treatment guidelines. First, for each mAb and indication, the exposure–response relation and target range of trough concentrations have to be established, preferably in prospective clinical trials. Second, the optimal timing and scope of mAb-TDM should be evaluated. Options for mAb-TDM timing can be once at treatment induction, intermittent during treatment maintenance, or at loss of response. Furthermore, it should be assessed whether all patients require TDM or if it is possible to apply mAb-TDM only in a preselected subgroup of patients most likely to benefit from TDM. Third, prospective randomized trials are needed to show mAb-TDM-guided clinical decision making superiority above standard care. Fourth, treatment algorithms for TDM-guided clinical decision making should be developed (**Figure 4**). In addition to clinical response and mAb concentration, ADA formation might also be included in the algorithm for clinical decision making in inflammatory disease.[48] Finally, there is a need for a standardized, validated, widely available, low cost, rapid, and easy analytical technique for mAb measurement. In the development and validation of analytical methods for mAb measurement, it should be verified that functionally active mAb concentrations are measured accurately and reliably. Measuring the functionally active mAb concentration is often challenging since mAbs in serum can be in complex with either the target antigen or ADAs. However, this complex bound fraction of the total mAb serum concentration is not functionally active but might be measured in the assay. Furthermore, functionally active concentration measuring is even more complicated when the treatment consists of two antibodies with the same target, such as trastuzumab with pertuzumab therapy for HER2-positive breast cancer. Currently, several methods are used to measure mAb concentrations and these include solid-phase enzyme-linked immunosorbent assay (ELISA), fluid-phase radioimmunoassay, fluid-phase mobility shift assay, and reporter gene assay. The most commonly used technique is ELISA and even within this technique there is a wide range of available assays and kits, hampering standardization. Moreover, ELISA is laborious and only available in a limited number of specialized laboratories, often requiring sample

logistics and delay. On-site point of care availability of a rapid and easy-to-use technique for measurement of mAb serum concentrations has the potential to boost implementation of mAb-TDM. The first pilot study with a handheld device for measuring infliximab concentrations showed promising results.[74] Additionally, the latest advances in lab-on-a-chip have resulted in miniaturized ELISA chips for HIV and prostate cancer diagnosis that outperformed conventional ELISAs on speed, costs, sample volume, and detection limit.[75] Application of the lab-on-a-chip concept by developing standardized mAb ELISA chips thereby holds promise for the future of mAb-TDM.

CONCLUSION

mAbs have considerable interpatient variability in pharmacokinetics and there are many factors influencing the serum concentration of an mAb. Exposure–response analyses are increasingly available for mAbs and these studies revealed that patients with low serum trough concentrations are at risk of treatment failure. Patients with high disease activity can be captured in a poor exposure–response cycle and are most in need of dose optimization. Current evidence from studies in inflammatory disease shows that TDM-guided dose optimization of anti-TNF-α mAbs has the potential to result in better disease control and is cost-effective. Available exposure–response data on antitumor mAbs suggests that in oncology, mAb dose optimization guided by TDM has at the least the beneficial potential seen with anti-TNF-α mAbs.

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AUTHOR CONTRIBUTIONS

T.H.O.M., M.J.H., L.I.S., K.L.L.M., and P.B.-V. wrote the manuscript; T.H.O.M. designed and performed the research.

CONFLICT OF INTEREST

L.I.S. has an academic position at the BIOS Lab on a Chip Group of the University of Twente. The other authors declare no conflicts of interest.

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