Immunogenicity and loss of response to TNF inhibitors: implications for rheumatoid arthritis treatment

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Key points

- Monoclonal antibodies and fusion proteins induce the formation of antidrug antibodies (ADAs), the occurrence and magnitude of which differs between chimeric antibodies, fully humanized antibodies and fusion proteins
- The clinical implication of ADAs are unclear, although ADAs are known to cause secondary drug failure
- Consensus definitions of primary and secondary non-response are lacking, as are evidence-based recommendations on how to guide biologic therapy on the basis of drug level and immunogenicity
- Testing for ADAs or serum trough drug levels might be indicated in some situations of primary and secondary treatment failure and could prompt changes in dosing or therapeutic agent
- When switching from an anti-TNF drug (originator) to a biosimilar of that originator, one has to take into consideration that ADAs against the originator will crossreact with the biosimilar, causing treatment failure
- More information regarding the immunogenicity of the different TNF antagonists and improved ADA testing systems could lead to the development of an immune-pharmacologic strategy for the individualized treatment of rheumatoid arthritis

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Adalimumab is a monoclonal antibody medication used to treat various autoimmune diseases, including rheumatoid arthritis, Crohn's disease, and psoriasis. Understanding its pharmacokinetics can help in its clinical use. Here are some key pharmacokinetic aspects of adalimumab:

Route of Administration: Adalimumab is typically administered as a subcutaneous injection.
Absorption: After subcutaneous injection, adalimumab is slowly absorbed into the bloodstream.
Peak Concentration (Cmax): Adalimumab reaches its maximum plasma concentration in about 5 days.

Distribution: Adalimumab is distributed throughout the body, including various tissues and compartments. **Its volume of distribution (Vd) is approximately 4.7 to 6.6 liters.**

Protein Binding: Adalimumab binds to proteins in the blood, primarily to immunoglobulin G1 (IgG1).

Metabolism: Adalimumab does not undergo significant metabolism in the body. It is broken down into small peptides and amino acids.

Elimination: **The elimination half-life (t½) of adalimumab is approximately 2 weeks**. This means it takes about 2 weeks for the concentration of adalimumab in the bloodstream to decrease by half.

Clearance: The clearance of adalimumab from the body is relatively slow, reflecting its long half-life.

Anti drug antibody may increase 4 fold the clearance and then reduce 4 fold the half life of adalimumab

Dosing: Due to its long half-life, adalimumab is typically administered at regular intervals (e.g., once every 1 to 2 weeks) to maintain therapeutic levels in the bloodstream.

Drug-Drug Interactions: Adalimumab is not known to have significant interactions with other drugs, but healthcare providers should be aware of potential interactions when prescribing multiple medications to a patient.

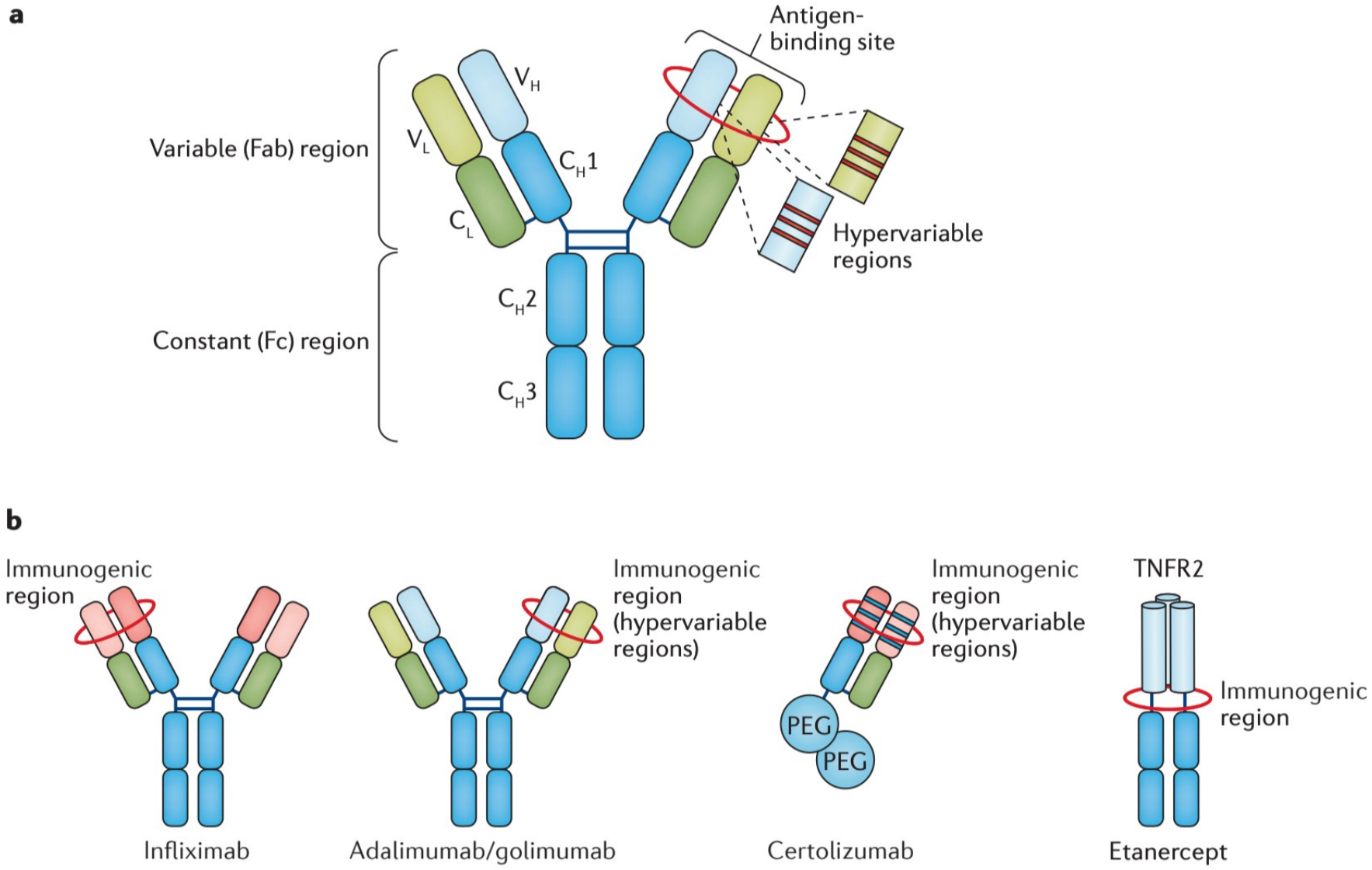

Figure 1 | **Structure of TNF antagonists. a** | Schematic representation of an antibody molecule. The Fc region is responsible for the effector functions of the antibody, and the Fab region forms the antigen-binding site. Within the variable regions are small areas of hypervariability, which determine antigen specificity. **b** | Anti-TNF antibody constructs used in the treatment of rheumatoid arthritis. Infliximab is a chimeric monoclonal antibody with a murine variable region (shown in red) fused to a human Fcγ1 Ig. Adalimumab and golimumab are fully human monoclonal antibodies. Certolizumab is a humanized Fab' fragment bound to polyethylene glycol (PEG) molecules. Etanercept is a TNF receptor–Fcγ1 fusion protein. Potentially immunogenic areas within each antibody construct are indicated in red. Abbreviations: C_H, constant heavy; C_L, constant light; TNFR2, TNF receptor 2; V_H, variable heavy; V_L, variable light.

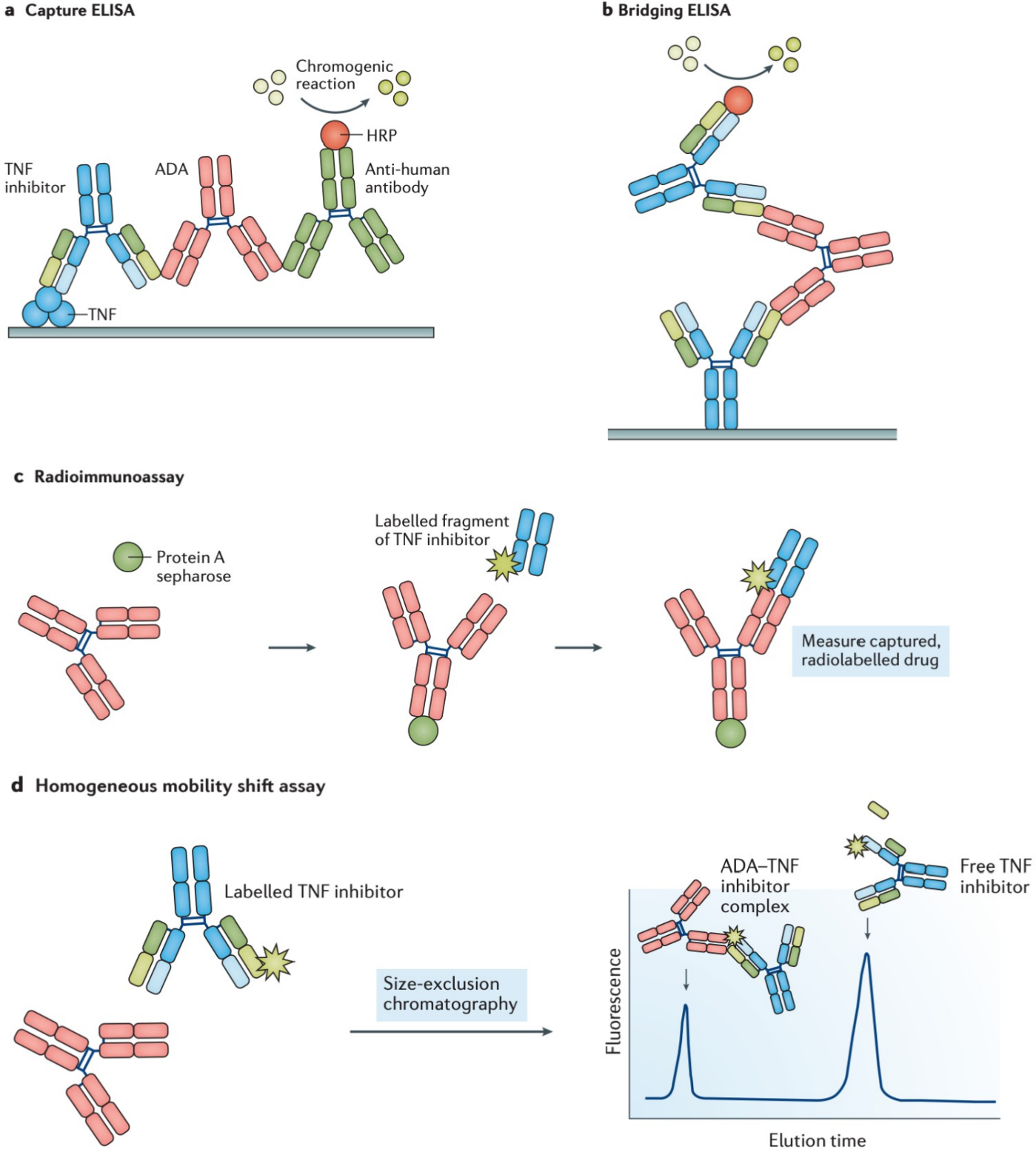

Figure 2 | Assays for detecting antidrug antibodies to TNF inhibitors. a | In a capture enzyme linked immunosorbent assay (ELISA), the TNF inhibitor is bound to TNF attached to the assay plate. Antidrug antibodies (ADAs) in the patient's serum bind to the drug, and are detected by horseradish peroxidase (HRP)-conjugated anti-human antibodies.
b | In a bridging ELISA, the assay plate is coated with the TNF inhibitor, which in turn bind ADAs. ADAs are detected by use of HRP-conjugated drug. Bridging ELISA is susceptible to interference by the drug and typically measures ADAs only in the absence of detectable drug levels. c | In a radioimmunoassay, protein A sepharose captures ADAs in the patient's serum, which then bind to radiolabelled drug, and the amount of radiolabelled drug is then measured. Radioimmunoassay can capture clinically relevant IgG1 and IgG4 antibodies. d | A homogenous mobility shift assay uses size-exclusion chromatography to measure ADA–drug complexes.

RA[17]. Finally, in an Italian study[18], the overall 10-year retention rate of first-line anti-TNF agents was ~23%, and was higher in patients with SpA than in patients with RA (30.5% versus 20.4%). Furthermore, etanercept was found to be the most persistent anti-TNF medication, with a higher drug survival rate than that of infliximab and adalimumab.

If ADAs are demonstrated, the question then arises of whether these antibodies could contribute to the loss of clinical efficacy of TNF antagonists by competing with TNF for the antigen-binding site. In this context, a study by van Schie *et al.*[64] demonstrated that in sera from 34 patients with RA treated with the anti-TNF antibodies adalimumab, golimumab or certolizumab pegol, more than 97% of ADAs were neutralizing antibodies. In 34 patients treated with infliximab, more than

Anti-adalimumab antibodies

Although adalimumab is a fully human monoclonal antibody, it still has immunogenicity. The frequency of the detection of anti-adalimumab antibodies in patients treated with adalimumab varies from 1% to 31% (TABLE 1), again most probably owing to the use of different assay systems. The antibodies against adalimumab are primarily anti-idiotypic antibodies, which elicit functional neutralization[68,69]. As with infliximab, trough levels of the therapeutic monoclonal antibody (adalimumab) are inversely associated with a loss of clinical efficacy[70–72]. It is worth mentioning that in these studies, adalimumab was given without concomitant immunosuppressive medication. Moving towards a personalized medicine approach, a 2013 study that included 221 patients with RA being treated with adalimumab demonstrated a relationship between adalimumab trough levels and clinical efficacy[73]. In this study, trough levels of 5–8 µg/ml were sufficient to elicit a clinical response. Importantly, these trough levels were substantially influenced by concomitant methotrexate medication[73].

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Long-term measurement of anti-adalimumab using pH-shift-anti-idiotype antigen binding test shows predictive value and transient antibody formation

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Results 53 out of 99 RA patients produced AAA. In 50 of these PIA positive patients, AAA could be detected within the first 28 weeks of treatment. Patients in which AAA could be detected in the PIA after 28 weeks of treatment were more prone to declining adalimumab levels (<5 μg/ml) ($p<0.01$) and high AAA levels which could be detected in the ABT ($p<0.05$) at later time points. We observed transient AAA formation in 17/53 patients.

Conclusions Results show that AAA develop early in treatment. However, levels that completely neutralise the drug may be reached much later in treatment. Furthermore, the patients positive for PIA at 28 weeks have an increased chance to develop clinical non-response due to immunogenicity. In some of the patients, AAA formation is transient.

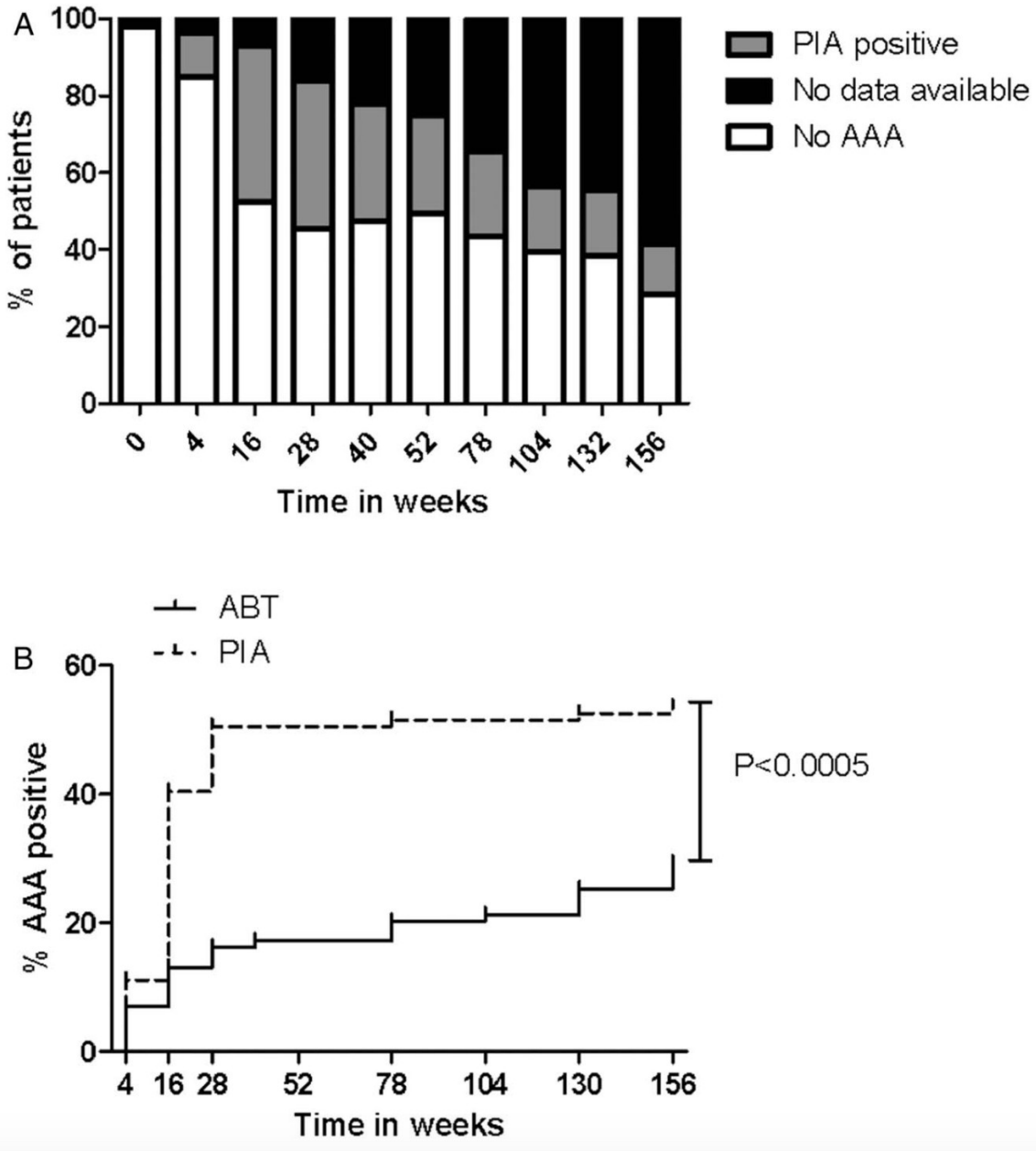

Figure 1 Long-term measurements of anti-adalimumab antibodies (AAA) in a group of 99 rheumatoid arthritis patients. (A) The number of patients in which AAA can be detected in the pH-shift-anti-idiotype ABT (PIA) (grey) or AAA negative patients (white) and the number of missing data (black) at the different time points during 3 years of follow-up. (B) The cumulative percentage of patients positive for AAA in the PIA (dotted line) and the antigen binding test (black line) during 3 years of adalimumab treatment. ABT, antigen binding test.

Baseline characteristics of patient population analyzed in subgroups regarding clinical disease activity in cd. X^2 chi-square; *t* test.

	Active Disease (n = 27)	**Clinical Remission (n = 62)**	***p*-Value**
Patients (N = 89)			
Age (years) (N = 89)	39 ± 14.8	45 ± 13.7	0.518
Duration of the disease (months) (N = 89)	112.6 ± 100.7	132.5 ± 104.5	0.874
Optimization time (months) (N = 31)	12.2 ± 9.1	17.9 ± 13.9	0.194
CRP (N = 77)	8.2 ± 8.2	1.8 ± 3.4	<0.05
ESR (N = 49)	35.6 ± 17.1	17.3 ± 20.8	0.705
Albumin (N = 50)	4.1 ± 0.46	4.1 ± 0.30	0.208
Hemoglobin (N = 76)	12.9 ± 1.9	13.2 ± 1.8	0.977
Hematocrit (N = 76)	38.7 ± 4.9	39.9 ± 4.6	0.624
Calprotectin (N = 63)	516 ± 397.9	231.9 ± 378.3	0.304
ADA serum level (N = 89)	10.2 ± 8.5	14.3 ± 9.4	0.395
ADA levels in optimized (Md ± SD)	10.5 ± 9.5	18.6 ± 8.9	
ADA levels in non-optimized (Md ± SD)	9.6 ± 6.8	13 ± 9.2	
	$p = 0.501$	$p = 0.894$	
BMI (N = 89)	24.1 ± 4.9	25.9 ± 5.2	0.854
HBI (N = 89)	8.6 ± 3	1.6 ± 1.5	<0.05

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Immunogenicity of TNF-Inhibitors

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molecule exchange (28), ADA of the IgG4 isotype will not be appropriately detected in these bridging formats, which may result in an underestimation of the ADA response. The ABT is different in that it uses a capture ligand (generally protein A) to immobilize specific and non-specific immunoglobulins present in the sample, which is followed by specific detection of the ADA using radiolabeled (in case of the radioimmunoassay, RIA) TNFi. For all these assays, drug-tolerant formats have been developed by employing acid pretreatment which dissociates the drug-ADA complexes that may be present in the sample.

An important patient-related risk-factor is the genetic background of a patient. Several studies have focused on variability in HLA-type and HLA alleles have been described to be associated with ADA formation (44–46). Some HLA alleles are thought to be protective against ADA formation (HLA-DQB1*05, HLA-DRB1*01, and HLA-DRB1*07, with odds ratios (OR) of 0.4 95% CI [0.186–0.862], 0.25 95% CI [0.073–0.927], and 0.2895% CI [0.078–1.004], respectively), while others might increase the risk of ADA formation (HLA-DRB1*03 and HLA-DRB*011, with OR of 2.52 95% CI [1.37–4.63] and 2.64 95% CI [1.240–4.045], respectively) (45). In a recently published study performed in 1240 Crohn's disease patients from the PANTS cohort the allele HLA-DQA1*05, which is carried by ~40% of the European population, was also associated with a significant higher rate of ADA development [hazard ratio 1.90 (1.60–2.25)] (46). The observation that some HLA alleles are associated with an increased risk for ADA formation against multiple TNFi is intriguing and has been suggested by some as supporting evidence for the role of HLA alleles in ADA development. However, no mechanism has yet been described that functionally explains this observation. In general, studies exploring the functional association between HLA alleles and ADA formation are highly desired.

Induction of Immune Tolerance

In some patients ADA responses are transient, which suggests a mechanism of immune tolerance. Immune tolerance refers to the absence of a measurable antibody response, skewing of the immune response to a less inflammatory phenotype, or exhaustion of the immune response to a particular immunogenic antigen. This physiological phenomenon is essential to prevent excessive immune responses to harmless antigens such as dietary antigens, allergens, and commensal microbiotics. The mechanisms contributing to immune tolerance have not yet been fully elucidated.

ADA AFFECTING THE PHARMACOKINETICS OF TNFi

All approved mAbs are intravenously (iv) or subcutaneously (sc) administered immunoglobulins of the IgG family. These exogenous IgG molecules are generally eliminated by the same mechanisms as their endogenous counterparts; both target-mediated drug disposition (TMDD) and nonspecific pino- and endocytosis have been described to contribute to the nonlinear and linear elimination of mAbs, respectively, eventually leading to proteolysis of the mAb. Pino- and endocytosis result in internalization of IgG molecules by fluid endocytosis or FcγR-mediated uptake, respectively, and contribute to the linear component of mAb clearance (71). However, not all

In contrast to target binding, binding of ADA to TNFi can alter elimination rates significantly. Increased clearance due to ADA may also be classified as target-mediated drug elimination. Ternant et al. specified that in the presence of detectable ADA, the clearance of adalimumab increases 5.5-fold at the population level (76). Berends et al. estimated an average 4-fold increase in clearance of adalimumab in the presence of detectable ADA (78). ADA detection thus seems to be one of the most important contributors to the pharmacokinetic variability seen for TNFi (42).

$T1/2 = (Ln2 \times Vd) / CL$

Explaining Interpatient Variability in Adalimumab Pharmacokinetics in Patients With Crohn's Disease

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Ther Drug Monit • Volume 40, Number 2, April 2018

Background: A significant proportion of patients with Crohn's disease (CD) require dose escalation or fail adalimumab (ADL) therapy over time. ADL, a monoclonal antibody directed against tumor necrosis factor, is approved for treatment of CD. Understanding pharmacokinetics (PK) of ADL is essential to optimize individual dosing in daily practice. The aim of this study was to evaluate PK of ADL in patients with CD and to identify factors that influence PK of ADL.

Methods: In a retrospective cohort study, the authors reviewed the charts of 96 patients with CD receiving ADL induction and maintenance treatment. This patient cohort was used for external validation of population pharmacokinetic models of ADL available from literature. In addition, a novel population PK model was developed using nonlinear mixed-effects modeling.

Results: None of the literature models properly described the PK of ADL in our cohort. Therefore, a novel population pharmacokinetic model was developed. Clearance of ADL increased 4-fold in the presence of anti-ADL antibodies. Patients who received ADL every week had a 40% higher clearance compared with patients receiving ADL every other week.

Conclusions: Clearance of ADL increased in the presence of anti-ADL antibodies and was associated with weekly ADL administrations. In clinical practice, the decision to intensify ADL treatment to weekly administrations is primarily based on disease activity. Increased disease activity may be the result of lower drug concentrations due to higher clearance. However, increased disease activity may also increase clearance due to increased target engagement. The causal relationship between these factors remains to be elucidated.

Key Words: adalimumab, Crohn's disease, inflammatory bowel disease, clinical pharmacology, population pharmacokinetics

(*Ther Drug Monit* 2018;40:202–211)

Population Pharmacokinetic Modeling

Two component model ; Vss 7 L = V1 4 L + V2 3 L
40 mg 5,7 microg/L with a Cmax 3 days after SC injection

Half life : 15-20 days