TDM monograph [Adalimumab]

Synonyms:

Humira, Hyrimoz, Hulio, Amgevita, Idacio, Imraldi, Yuflyma

Summary

Indication:	Rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, axial spondyloarthritis, uveitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis, and hidradenitis suppurativa. Off-label indications: Autoinflammatory conditions in children that do not respond to conventional treatment, including sarcoidosis, Blau syndrome, chronic recurrent multifocal osteomyelitis/synovitis, acne, pustulosis, hyperostosis, and ostitis (NKFK) Indication TDM: Inflammatory rheumatic diseases and inflammatory bowel diseases
Sample material:	Serum or Plasma (sometimes microsampling also feasible)
Time of sampling:	Trough concentration
Storage conditions:	Fridge (2-8°C) or roomtemperature (maximum of 3 days)
Interpretation:	-
Evidence level:	2

Contents

Introduction

Adalimumab is a human immunoglobulin G1 monoclonal antibody that binds specifically and with high affinity to both soluble and transmembrane forms of Tumor Necrosis Factor α (TNF-α), but not to lymphotoxin (TNFβ) (1). Binding to TNF-α neutralizes the biological function of this cytokine by blocking the interaction of TNF-α with p55 and p75-TNF receptors on the cell surface (1). Adalimumab inhibits the binding of TNF-α to its receptor, thereby reducing the activation of "Nuclear Factor Kappa B" (NF-κB) and the subsequent inflammatory response (2, 3). Adalimumab also has cytotoxic properties against cells that express TNF-α, thereby inducing apoptosis (2, 3). The biological response regulated by TNF-α is also modulated by adalimumab, including changes in the concentrations of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1 and ICAM-1). Adalimumab is used in inflammatory conditions and belongs to the so-called "Biologicals" (1).

Dosing guidelines

The dosage of adalimumab varies by indication and age.

Rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis

The standard dosage for adults is 40 mg subcutaneously once every 2 weeks (2, 4). In case of no clinical response after 12 weeks of treatment, continuation of treatment should be reconsidered. start with a dosage of 40 mg or 80 mg and then continue with 40 mg once every two weeks (3-5). Maintenance treatment may be increased to 40 mg each week when there is insufficient or lack of response (3, 4).

Crohn's disease

Adult induction schedule: 80 mg in 1 dose at week 0 and 40 mg in 1 dose at week 2; a faster induction schedule is 160 mg at week 0 and 80 mg at 1 dose at week 2; the dose of 160 mg is given as 4 injections per day or as 2 injections per day on 2 consecutive days; the 80 mg dose is administered as 2 injections in 1 day; maintenance dose adults 40 mg 1x every 2 weeks, if necessary 40 mg 1x per week or 80 mg 1x every 2 weeks; If adalimumab has been discontinued and symptoms reappear, adalimumab may be re-administered (4, 6).

Ulcerative colitis

Adult induction schedule: 160 mg at week 0 and 80 mg at week 2, the dose of 160 mg is administered as 4 injections on 1 day or as 2 injections per day on 2 consecutive days; the 80 mg dose is administered as 2 injections in 1 day; maintenance dose adults 40 mg 1x every 2 weeks, in case of reduced clinical response 40 mg 1x weekly or 80 mg 1x every 2 weeks; If there is no clinical response after 2-8 weeks of treatment, treatment should be discontinued (4, 6).

Uveitis

Adults starting dose 80 mg, followed by 40 mg after 1 week 1x every 2 weeks; If a corticosteroid is used, it can be tapered off, starting 2 weeks after starting adalimumab (4, 6).

Plaque psoriasis,

Adults starting dose: 80 mg, followed by 40 mg after 1 week 1x every 2 weeks; If there is no clinical response after 16 weeks of treatment, it may be considered to increase this to 40 mg 1x per week or 80 mg 1x every 2 weeks; If there is sufficient response, continuation of treatment with 40 mg 1x every 2 weeks may be considered (4, 6).

Hidradenitis suppurativa.

Adults induction schedule: 160 mg at week 0 and 80 mg at week 2, the dose of 160 mg is administered as 4 injections in 1 day or as 2 injections per day on 2 consecutive days, the dose of 80 mg is administered as 2 injections in 1 day; after 2 weeks maintenance dose adults 40 mg 1x per week or 80 mg 1x every 2 weeks; in case of no clinical response after 12 weeks of treatment, continuation of treatment should be reconsidered; In case of an interruption, adalimumab can be restarted with 40 mg 1x weekly or 80 mg 1x every 2 weeks;

Dosing guidelines in children and adolescents

In children with arthritis, uveitis or psoriasis under 30 kg body weight, the dosage is 20 mg every 2 weeks. Above 30 kg body weight, the dosage is 40 mg every 2 weeks(4, 6).

Children with IBD, with a body weight below 40 kg, will start with 40 mg at week 0 and 20 mg at week 2. The maintenance dosage is 20 mg every 2 weeks (4, 6).

In adolescents under 30 kg body weight, the starting dose is 80 mg at week 0, followed by 40 mg every 2 weeks from week 1. In case of insufficient response, the dosage may be increased to 40 mg per week or 80 mg every 2 weeks (4, 6).

For more details about dosing in children and adolescents per indication see SmPC(4)

Dosing guidelines in patients with altered pharmacokinetics

N.A.

Indications/Criteria for TDM

Improvement of efficacy and reduction of drug expenses

Reference values

Efficacy

Indication	Lower limit	Upper Limit
Rheumatoid arthritis (7)	5,0 mg/L	8,0 mg/L
Rheumatoid arthritis (2, 8)	4,0 mg/L	8,0 mg/L
Crohn's disease (9)	>4,5 mg/L	
Crohn's disease (10)	>5,85 mg/L	
Ulcerative colitis (9)	>4,5 mg/L	
IBD (10-12)	>5,0 mg/L	12 mg/L
Plaque psoriasis (13)	3,51 mg/L	7,00 mg/L

Relationship with occurrence of side effects

-

Toxicity

No relationships between toxicity/adverse events and adalimumab serum concentrations were found. There does seem to be a relationship between the dose and the risk of infections. The highest dose evaluated consisted of several intravenous doses of 10 mg/kg, which corresponds approximately to 15 times the recommended dose (4). Side effects that are common with the use of adalimumab include respiratory tract infections, leukopenia, neutropenia, headache, nausea and vomiting, abdominal pain, muscle pain, and injection site reactions (3).

Sampling conditions

In maintenance treatment, a trough level is measured under steady state conditions. The determination takes place in serum (14). The sample should be kept cool (2-8°C), but may be shipped at room temperature.

Additional information concerning the interpretation of results

Several observational studies at the population level have shown a relationship between serum levels of adalimumab (whether or not in the presence of antibodies) and response (1, 12, 15). The adalimumab levels could potentially be useful to individualize treatment with adalimumab. This individualization would then consist of increasing the dose, adding an immune modulator to affect clearance, switching to another drug class, or switching to another biological class or not (15). These choices depend on the treatment options, so the interpretation of the results depends on the indication of adalimumab. There are several studies that endorse the importance of measuring the concentrations of adalimumab and antidrug antibodies (ADAs) in order to optimize the dosing schedule (15).
Adalimumab serum levels of >5 mg/L are generally found in patients with a good response to treatment (16). The trough levels of patients with no response are often much lower or even undetectable (16). The normal dosing schedule may lead to a maximum trough level of adalimumab of 30 mg/L (16). Although the relationship with toxicity remains unclear, higher trough levels do not appear to lead to increased effectiveness (16). For safety and cost reduction, adalimumab >12 mg/L down-titration may be considered at trough levels. The therapeutic range of adalimumab is estimated to be between 5 and 12 mg/L (16).

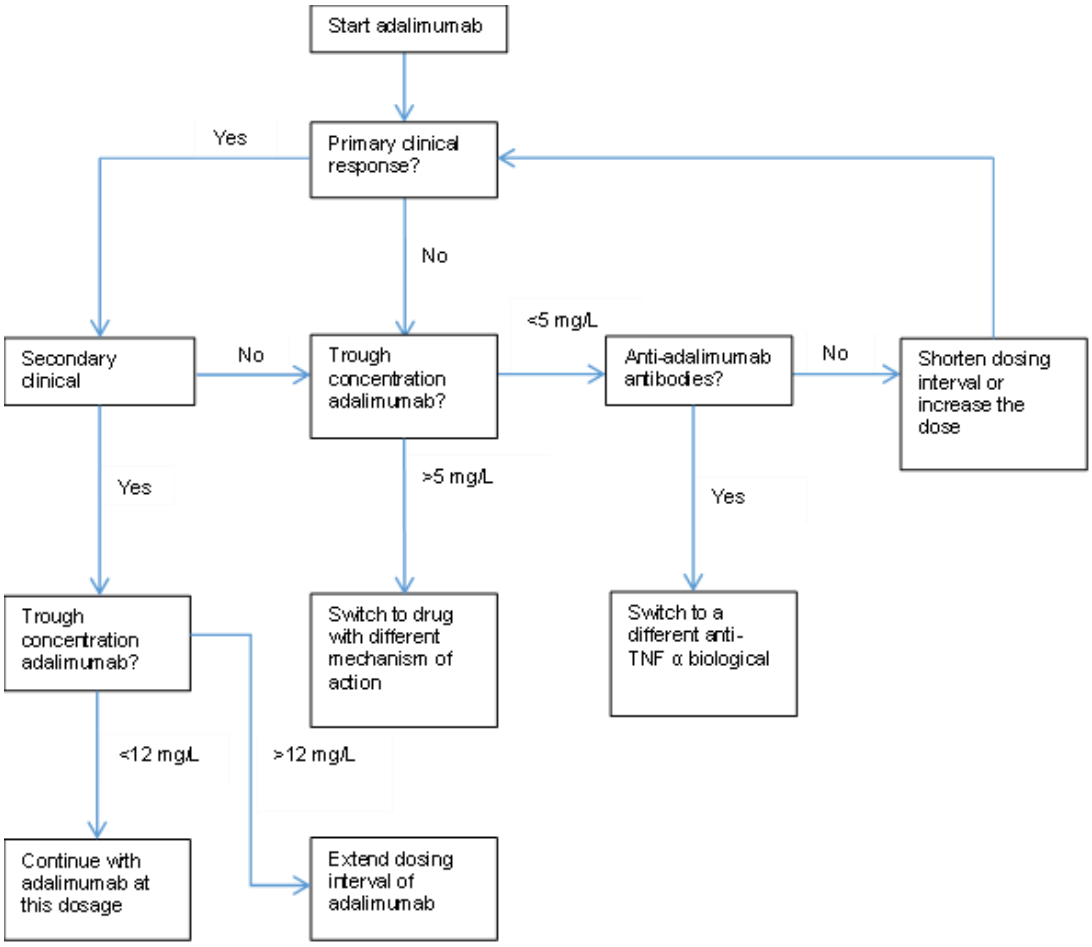

Figure 1: flowchart that may help optimize the treatment of a patient currently taking adalimumab.

Inflammatory rheumatic diseases

Proactively determining adalimumab levels is not yet widely recommended in daily practice. Measuring serum levels is only used as an aid in the evaluation of treatment (15). Adalimumab gives improvement in both joint and skin manifestations of the disease. The lack of response to adalimumab is probably due to the formation of ADAs (17). These ADAs affect the serum concentration of adalimumab and thereby alter the clinical response (17). Anti-TNF-α therapy is costly, which is why it is important to track down non-responders for any dose adjustment and determine the effectiveness of adalimumab (17). Positive ADA titers have been measured in rheumatoid arthritis after adalimumab use, ranging from 5% to 54% (18). Positive ADA titers have been measured in rheumatoid arthritis after adalimumab use, ranging from 5% to 54%. In rheumatology, the dosage is not increased in case of insufficient response, because more cost-effective strategies are available, such as switching to another bDMARD. This is because the chance of a response with another bDMARD is greater than when the dosage of adalimumab is increased. In addition, increasing the dosage is more expensive than starting with another bDMARD in the registered dosage. Thus, TDM could not be used to see if higher doses are more effective in a patient (19). There is evidence that TDM can be used to select an alternative bDMARD to switch to in case of non-response to adalimumab. If the patient has ADAs formation, it may be considered to switch to a drug with a different target point. It is possible that anti-drug antibodies will be formed again against another TNF-α-blocking agent (19). If this happens, one can choose from a drug that does not belong to the TNF group.

Inflammatory bowel disease

Adalimumab has been shown to be effective in the treatment of inflammatory bowel disease. However, there are relatively many patients for whom the treatment does not have an effect. Possibly this could be a result of ADA formation. In inflammatory bowel disease, positive ADA titers range from 9% to 46% (18). An adalimumab level >5.85 mg/L predicts a combination of clinical and biochemical remission (10). A serum adalimumab level of 7.1 mg/L is correlated with mucosa healing in patients with IBD with 85% specificity and 32% sensitivity (12). Higher adalimumab levels achieve a higher rate of mucosa healing with substantial gains when serum concentrations increase between 0 mg/L and 8 mg/L (12). A plateau is reached in terms of mucosal healing at a level of 12 mg/L (12, 20-24). Adalimumab concentrations ≥12 mg/L are associated with histological remission in patients with Crohn's disease (25). Serum levels of adalimumab <3 mg/L are associated with increased inflammation and an increase in CRP concentrations, and levels <4.9 mg/L were associated with higher CRP and FCP levels (26) and predicts that there will be no cure of the mucosa (11, 27). When there is a lack of response and the trough level of adalimumab is >4.5 mg/L, this is an indication that dose increase in patients is not useful (9). A trough level of >4.5 mg/L is considered adequate and provides a good prediction of symptomatic treatment (9). High ADA titers of more than 4 micrograms per ml equivalent indicate that intensification of dosing is not useful (9). A dose increase gives a longer duration of response in patients with no or low ADA titer compared to patients with a high ADA titer (9). An alternative intervention in the absence of response is to switch to another anti-TNF therapy. Patients with high ADA titers have been shown to have a longer response time on an anti-TNF switch compared to a dose increase (9). In contrast, patients without ADA or with low titer responded better to a dose increase than to an anti-TNF switch (9). However, after a dose increase, the concentration of ADA did increase in patients without/with a low ADA titer previously (9). When there is an adequate adalimumab

trough level, but there is no good response, it is better to switch to a drug from a different group than to try to optimize the anti-TNF therapy (9).

	No/low antibodies detectable against adalimumab*	**High antibody titers detectable against adalimumab**
Adalimumab <4 mg/L	Decrease dosing interval or increase dosage.	Switch to another agent within the anti-TNF group.
Adalimumab 4-8 mg/L	In case of partial response, a reduction in the dosing interval or increase in the dose may be considered, but this will have to be considered on a patient-by-patient basis.	
Adalimumab >8 mg/L	Switch to a drug outside the anti-TNF group in the absence of response.	

*Cut-off value depends on the determination method used. When using radioimmune assay (RIA) cut-off limit 12AE/mL (AE=arbitrary units) (9, 18)

If there is no clinical indication to determine adalimumab, this is not useful. There are studies that show that patients with sufficient/adequate clinical response have transient ADAs during treatment. In such cases, TDM could possibly lead to the wrong decision that adalimumab should be replaced. TDM and the determination of ADAs are becoming increasingly important to optimize a patient's treatment (28). Also proactive TDM has shown benefit over standard of care (21-23, 29). The determination of trough levels and the concentration of ADAs in patients with no clinical response may help to distinguish between non-adherence, immunogenicity, and non-immune clearance of adalimumab or uncontrolled inflammation despite adequate therapy with adalimumab (28).

Indications other than inflammatory bowel and rheumatic diseases
Adalimumab has been shown to be effective in treating plaque psoriasis, improving quality of life (30). In the treatment of plaque psoriasis, a steady state concentration of 5.2 mg/L was found to be effective (30). The formation of ADAs significantly decreases the serum concentration of adalimumab and these patients have twice as high clearance of adalimumab compared to patients without ADA formation (30). TDM could also be applied here (31). The positive ADA titers in ankylosing spondylitis, plaque psoriasis and psoriatic arthritis range from 18% to 45% (18). These titers do not differ much from those measured when taking infliximab, so it may not be useful to switch to this anti-TNF-α therapy (18).

Background information [extended]

The role of adalimumab concentration measurements

After administration of adalimumab, a large variability in clinical response and trough levels is observed, with a significantly higher serum concentration of adalimumab being seen in patients with a good response (13). A large interindividual variation in pharmacokinetics of adalimumab is observed (13, 32). Intra-patient variation appears to be limited (33). The amount of TNF varies greatly between patients and also at the site of inflammation, so the minimum effective dose can be different for each patient (32). TDM could optimize treatment by measuring adalimumab levels and ADAs concentrations (14). At the moment, measuring the adalimumab level seems to be the most relevant (14). ADAs can then be determined as a second step and

play more of a role in finding a cause for the low or undetectable adalimumab levels (14). The ultimate goal of TDM is personalized medicine, potentially increasing effectiveness and reducing costs (14).
The effectiveness of adalimumab is associated with serum levels of adalimumab and with serum levels of antibody antibodies (ADAs) against adalimumab (1, 12). Thus, the presence of ADAs determines the immunogenicity of adalimumab. These ADAs neutralize the antibodies and thus the pharmacological action (1). If the effectiveness of adalimumab is insufficient, ADAs are a possible explanation. In the absence of response to adalimumab or at low serum concentrations, the concentration of ADAs could be determined (34). ADAs reduce the effectiveness of adalimumab by competing for the cytokine binding site (neutralizing the antibodies) or by stimulating rapid drug clearance (non-neutralizing/binding antibodies (34). It is still unclear why some patients form ADAs and others do not (35). The patients who develop ADAs usually do so within the first 6 to 12 months of treatment (34, 35). However, measurable ADAs can also develop only after years of treatment (35). ADA titers may increase after the first injection of adalimumab and decrease after discontinuation of adalimumab (18). In some patients, ADA titers also decrease with adalimumab continuation (18). Not only does the formation of ADAs lead to a lack of response, a higher TNF level can also be an explanation for this (28).
There are also other factors that increase the interindividual variability in the pharmacokinetics of adalimumab, such as the properties of the disease (the amount of TNF α at the site of inflammation varies from patient to patient), co-medication (methotrexate may be able to influence that clearance of adalimumab) and the characteristics of the patient itself (genetic variability) (32, 36).
When low adalimumab serum concentrations are measured, it can be decided to measure the concentration of ADAs. With a high serum concentration of adalimumab, a dose reduction or an extension of the dosing interval may occur (8).

Adalimumab bioanalysis methods
Adalimumab serum levels can be analytically determined in several ways, of which the Enzyme-Linked Immunosorbent Assay (ELISA) is the most commonly used (1). Other quantitative determination methods, such as LC-MS/MS, have also been described and are in use (37, 38). Currently even methods using fingerprick samples are operational (39).
Serum levels of ADA can be analytically determined in multiple ways, with the double antigen ELISA and the radioimmunoassay (RIA) being the most commonly used (1, 12, 15, 34). The RIA cannot measure bound ADAs to adalimumab and therefore the amount of ADAs formed may be underestimated (13). The method to determine the ADAs must be validated and sufficiently sensitive, otherwise the results cannot be used. However, these are relative quantifications compared to a chosen ADA standard, these are usually not compared between different laboratories. As a result, the results from different laboratories cannot be compared, and must be interpreted on the basis of literature describing the same method. ADA determinations can be done when there is a low adalimumab level (<5 mg/L).

Biosimilars
Kromeya (Merck) is a biosimilar to adalimumab. Kromeya shares an identical amino acid sequence with the reference product Humira (adalimumab). The biosimilar shows the same concentration-time profile as adalimumab, and there is pharmacokinetic equivalence. The AUC parameters of this biosimilar are 89-96% similar to those of adalimumab. The half-life of MSB11022 is shorter than that of adalimumab (12 days vs. 14.5 days), but there is a large inter-individual variability in the half-life. Antibodies to adalimumab are found in 14.1% of cases after administration of MSB11022, compared to 12.7% after administration of

adalimumab (EU-registered Humira). The number of adverse reactions that occurred did not differ between the two drugs, with most of the side effects also being mild in nature (1).
Another biosimilar of adalimumab is Amjevita (Amgen Inc.) (40, 41). It has the same amino acid sequence as adalimumab and in addition to that, it has the same pharmaceutical form and dosage strength. However, the formulation of adalimumab contains other excipients, including other buffer components and stabilizers (40, 41). The mean concentration-time profiles are similar between Amjevita and adalimumab. There is bioequivalence between the biosimilar and adalimumab in terms of AUC and tmax. ADAs are formed in 54%, 55% and 67% of cases, respectively after administration of Amjevita, adalimumab US and adalimumab EU. Neutralizing antibodies are found in 18%, 22% and 21% of participants, respectively after administration of Amjevita, adalimumab VS and adalimumab EU. The adalimumab biosimilar Exemtia (Zydus) has also shown bioequivalence (42). This biosimilar shows an almost equal binding affinity (42). In addition, the effectiveness and safety of this biosimilar has been demonstrated in patients with rheumatoid arthritis who are also on maintenance treatment with methotrexate (27). It turned out that the same number of ADAs were formed in both the biosimilar and the original (27). Biosimilar Imraldi (Samsung Bioepis) has an identical amino acid sequence and psychogenic and in vitro properties as adalimumab. The incidence of ADAs during treatment with SB5 is similar to that during treatment with adalimumab (33.1% vs 32.0%) (43). The effectiveness, safety and immunogenicity of biosimilar BI 695501 (Boehringer Ingelheim) are also similar to those of adalimumab in patients with RA. PK bioequivalence was demonstrated in terms of AUC and tmax (43).

Pharmacodynamics

Adalimumab binds to soluble and membrane-bound TNF-α, preventing its interaction with TNF receptors on the cell surface. This binding inhibits the downstream signaling pathways responsible for the inflammatory response, ultimately reducing inflammation and disease activity.

Pharmacokinetics

Adalimumab shows linear pharmacokinetics. After subcutaneous administration of a single dose of 40 mg, the peak concentration in serum is reached after approximately 5 days after administration and has an average bioavailability of 64% (1, 44). The average half-life is 2 weeks (1). This half-life of 2 weeks is also found in patients with IBD, where it can range from 10 to 20 days (32). The clinical effect of adalimumab occurs after a few weeks. When a dose of 40 mg subcutaneously is used once every two weeks for the treatment of adults with non-infectious uveitis or, the mean steady state concentration is 5.5 mg/L (45, 46). The steady state concentration is usually between 4 and 8 mg/L (2). Although the therapeutic range is estimated to be between 5 and 12 mg/L (16). At the right dosing frequencies and administration of adalimumab, it provides a uniform concentration-time profile due to the slow absorption rate from subcutaneous tissue in combination with the slow elimination rate (46).
Adalimumab is not bound to plasma proteins (36). The distribution depends on the limited ability to diffuse across the cell membranes (36). Adalimumab is a large molecule and quite polar, therefore the diffusing will not take place by transcellular diffusion. Adalimumab has a low diffusion capacity and therefore the steady state concentration in the interstitial fluid is much lower than in the circulation. As a result, the distribution volume is relatively small and is approximately equal to the plasma volume, regardless of the dosage used (36). In addition, TNF may have concentration gradients in different compartments, so that binding of adalimumab to TNF may lead to redistribution and a change in the pharmacokinetic profile (32).

The clearance of antibodies such as adalimumab can take place in different ways, but the exact mechanisms are not well described. The following are a few of the possible clearance mechanisms:

- Proteolytic catabolism. Although it is still unclear exactly where this process takes place, it probably occurs in many cell types. Adalimumab binds to an Fcγ receptor, causing it to be taken up by a phagocyte and then transported into a lysosome and broken down (32). There may be interindividual variability in clearance via Fcγ receptors due to different polymorphisms of the receptor (44).
- “Antigen sink”. In this process, adalimumab binds to a membrane-bound antigen, causing it to be absorbed by the cell and degraded into lysosomes. This clearance pathway can become saturated when high doses of adalimumab are administered (32).

Clearance can also be affected by neonatal Fc receptors (FcRn). These FcRn are mainly expressed on vascular endothelial cells or cells of the reticuloendothelial system, such as phagocytic cells. The FRn serve as a recycling and protection mechanism to extend the half-life of IgG. FRn binds adalimumab that is bound to an antigen, after which the complex is absorbed into the cell, where the antigen is broken down. Then, depending on the pH, adalimumab is returned to the cell surface and released into circulation (32, 44). Adalimumab concentrations are highly variable between and within individual patients. There are also a number of factors that may affect the pharmacokinetics. For example, the amount of TNF-α at the site of inflammation and in the circulation (depending on disease activity) is different in each patient, but the amount can also vary within the patient over time. In addition, adalimumab is cleared faster when ADAs have formed. The formation of ADAs results in lower serum adalimumab levels, which means that the dosage must be increased. Adalimumab clearance is also decreased with combination therapy with methotrexate. In conclusion, the main causes of the variable clearance of adalimumab between and within patients are the patient characteristics such as body weight and albumin, disease activity (CRP and rheumatoid factor), co-medication, and the formation of ADAs.

Pharmacogenetics

No application yet.

Interactions

A combination of adalimumab with anakinra or abatacept (or other IL-1 inhibitor) is not recommended, as a higher incidence of serious infections has been observed than with monotherapy. There may be a pharmacodynamic interaction (3). Methotrexate may be able to reduce the expression of Fcγ receptors on the membrane of phagocytic cells and reduce the formation of antibodies against adalimumab (32). As a result, the clearance of adalimumab is lowered and serum levels increase. The clearance of adalimumab may be reduced by up to 44% in combination with methotrexate (32). The plasma concentration of adalimumab is higher in combination with methotrexate than with monotherapy.

PK parameters

	F (%)	**Cl** (L/day^{-1})	**Vd** (L)	$t_{1/2}$ (days)	Protein binding	Tmax (days)	Ref.
Adults RA/IBD (IV)	100	0.3 - 0.6	4.7-6.1	10-14	-	0.1	(1, 4, 6, 36, 45, 46)
Adults RA/IBD (SC)	64	0.28 – 0.42	4.7-6.1	10-14		5	(1, 4, 6, 36, 45, 46)

Population models

Population	**k_a (day^{-1})**	**Cl (L/day)**	**IIV (CV%)**	**V_1 (L)**	**IIV (CV%)**	**$T_{1/2}$ (days)**	**Proportional error (%)**	
Rheumatoid arthritis	0.28	0.32	17	10.8	92	-	24	(5)
Plaque psoriasis	0.63	0.586	62	11.4	43.6	-	-	(30)
Crohn's disease	0.15	0.42	65	13.5	48	22 ADA- 4.1 ADA+	15	(47)
Crohn's disease in children	0.200	0.281	45.9	4.750	-	-	-	(48)
EMEA Humira volwassenen		0.37*						(6)
EMEA Humira kinderen		0.28**						(6)

*This is the estimated CL/F in a patient with a body weight of 73 kg. Clearance is weight-dependent.
** The mean Cl/F was 2.5 times higher in ADA+ individuals compared to ADA individuals.

Literatuur

1. Hyland E, Mant T, Vlachos P, Attkins N, Ullmann M, Roy S, et al. Comparison of the pharmacokinetics, safety, and immunogenicity of MSB11022, a biosimilar of adalimumab, with Humira((R)) in healthy subjects. Br J Clin Pharmacol. 2016;82(4):983-93.
2. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117(2):244-79.
3. Adalimumab Monografie [Internet]. 2023 [cited 20-12-2023]. Available from: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2900.html.
4. Agency EM. SmPC adalimumab [Available from: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf.

5. Ternant D, Ducourau E, Fuzibet P, Vignault C, Watier H, Lequerre T, et al. Pharmacokinetics and concentration-effect relationship of adalimumab in rheumatoid arthritis. Br J Clin Pharmacol. 2015;79(2):286-97.
6. Agency EM. Assesment Report Humira, Adalimumab 2017 [updated 12-10-2017. Available from: https://www.ema.europa.eu/en/documents/variation-report/humira-h-c-481-x-164g-epar-assessment-report-variation_en.pdf.
7. Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, Rispens T, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. Ann Rheum Dis. 2015;74(3):513-8.
8. Rosas J, Llinares-Tello F, de la Torre I, Santos-Ramirez C, Senabre-Gallego JM, Valor L, et al. Clinical relevance of monitoring serum levels of adalimumab in patients with rheumatoid arthritis in daily practice. Clin Exp Rheumatol. 2014;32(6):942-8.
9. Yanai H, Lichtenstein L, Assa A, Mazor Y, Weiss B, Levine A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. Clin Gastroenterol Hepatol. 2015;13(3):522-30 e2.
10. Mazor Y, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther. 2014;40(6):620-8.
11. Roblin X, Marotte H, Rinaudo M, Del Tedesco E, Moreau A, Phelip JM, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2014;12(1):80-4 e2.
12. Ungar B, Levy I, Yavne Y, Yavzori M, Picard O, Fudim E, et al. Optimizing Anti-TNF-alpha Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2016;14(4):550-7 e2.
13. Menting SP, Coussens E, Pouw MF, van den Reek JM, Temmerman L, Boonen H, et al. Developing a Therapeutic Range of Adalimumab Serum Concentrations in Management of Psoriasis: A Step Toward Personalized Treatment. JAMA Dermatol. 2015;151(6):616-22.
14. van Bezooijen JS, Koch BC, van Doorn MB, Prens EP, van Gelder T, Schreurs MW. Comparison of Three Assays to Quantify Infliximab, Adalimumab, and Etanercept Serum Concentrations. Ther Drug Monit. 2016;38(4):432-8.
15. Silva-Ferreira F, Afonso J, Pinto-Lopes P, Magro F. A Systematic Review on Infliximab and Adalimumab Drug Monitoring: Levels, Clinical Outcomes and Assays. Inflamm Bowel Dis. 2016;22(9):2289-301.
16. Zandvliet ML, van Bezooijen JS, Bos MA, Prens EP, van Doorn M, Bijen I, et al. Monitoring antigen-specific biologics: current knowledge and future prospects. Ther Drug Monit. 2013;35(5):588-94.
17. Chimenti MS, Triggianese P, Narcisi A, Marinari B, Teoli M, Faleri S, et al. Long-term treatment with adalimumab in psoriatic arthritis: serum adalimumab concentration, immunogenicity and the link with clinical response. J Int Med Res. 2016;44(1 suppl):48-52.
18. Meroni PL, Valentini G, Ayala F, Cattaneo A, Valesini G. New strategies to address the pharmacodynamics and pharmacokinetics of tumor necrosis factor (TNF) inhibitors: A systematic analysis. Autoimmun Rev. 2015;14(9):812-29.
19. Reumatologie NVv. Richtlijn verantwoord gebruik van biologicals. 2011.

20. Irving PM, Gecse KB. Optimizing Therapies Using Therapeutic Drug Monitoring: Current Strategies Future Perspectives. Gastroenterology. 2022;162(5):1512-24.
21. Albader F, Golovics PA, Gonczi L, Bessissow T, Afif W, Lakatos PL. Therapeutic drug monitoring in inflammatory bowel disease: The dawn of reactive monitoring. World J Gastroenterol. 2021;27(37):6231-47.
22. Wu JF. Therapeutic Drug Monitoring of Biologics for Patients with Inflammatory Bowel Diseases: How, When, and for Whom? Gut Liver. 2022;16(4):515-24.
23. Cheifetz AS, Abreu MT, Afif W, Cross RK, Dubinsky MC, Loftus EV, Jr., et al. A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease. Am J Gastroenterol. 2021;116(10):2014-25.
24. Bourchany A, Gilletta De Saint-Joseph C, Breton A, Barreau F, Mas E. Optimization of biologics to reduce treatment failure in inflammatory bowel diseases. Curr Opin Pharmacol. 2020;54:51-8.
25. Juncadella A, Papamichael K, Vaughn BP, Cheifetz AS. Maintenance Adalimumab Concentrations Are Associated with Biochemical, Endoscopic, and Histologic Remission in Inflammatory Bowel Disease. Dig Dis Sci. 2018;63(11):3067-73.
26. Carlsen A, Omdal R, Leitao KO, Isaksen K, Hetta AK, Karlsen LN, et al. Subtherapeutic concentrations of infliximab and adalimumab are associated with increased disease activity in Crohn's disease. Therap Adv Gastroenterol. 2018;11:1756284818759930.
27. Jani RH, Gupta R, Bhatia G, Rathi G, Ashok Kumar P, Sharma R, et al. A prospective, randomized, double-blind, multicentre, parallel-group, active controlled study to compare efficacy and safety of biosimilar adalimumab (Exemptia; ZRC-3197) and adalimumab (Humira) in patients with rheumatoid arthritis. Int J Rheum Dis. 2016;19(11):1157-68.
28. Bodini G, Giannini EG, Savarino V, Del Nero L, Pellegatta G, De Maria C, et al. Adalimumab trough serum levels and anti-adalimumab antibodies in the long-term clinical outcome of patients with Crohn's disease. Scand J Gastroenterol. 2016;51(9):1081-6.
29. Papamichael K, Juncadella A, Wong D, Rakowsky S, Sattler LA, Campbell JP, et al. Proactive Therapeutic Drug Monitoring of Adalimumab Is Associated With Better Long-term Outcomes Compared With Standard of Care in Patients With Inflammatory Bowel Disease. J Crohns Colitis. 2019;13(8):976-81.
30. Mostafa NM, Nader AM, Noertersheuser P, Okun M, Awni WM. Impact of immunogenicity on pharmacokinetics, efficacy and safety of adalimumab in adult patients with moderate to severe chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2017;31(3):490-7.
31. Liau MM, Oon HH. Therapeutic drug monitoring of biologics in psoriasis. Biologics. 2019;13:127-32.
32. Colombel JF, Feagan BG, Sandborn WJ, Van Assche G, Robinson AM. Therapeutic drug monitoring of biologics for inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(2):349-58.
33. Ward MG, Thwaites PA, Beswick L, Hogg J, Rosella G, Van Langenberg D, et al. Intra-patient variability in adalimumab drug levels within and between cycles in Crohn's disease. Aliment Pharmacol Ther. 2017;45(8):1135-45.
34. Jani M, Isaacs JD, Morgan AW, Wilson AG, Plant D, Hyrich KL, et al. Detection of anti-drug antibodies using a bridging ELISA compared with radioimmunoassay in adalimumab-treated rheumatoid arthritis patients with random drug levels. Rheumatology (Oxford). 2016;55(11):2050-5.

35. Eng GP, Bouchelouche P, Bartels EM, Bliddal H, Bendtzen K, Stoltenberg M. Anti-Drug Antibodies, Drug Levels, Interleukin-6 and Soluble TNF Receptors in Rheumatoid Arthritis Patients during the First 6 Months of Treatment with Adalimumab or Infliximab: A Descriptive Cohort Study. PLoS One. 2016;11(9):e0162316.
36. Ferri N, Bellosta S, Baldessin L, Boccia D, Racagni G, Corsini A. Pharmacokinetics interactions of monoclonal antibodies. Pharmacol Res. 2016;111:592-9.
37. Jourdil JF, Nemoz B, Gautier-Veyret E, Romero C, Stanke-Labesque F. Simultaneous Quantification of Adalimumab and Infliximab in Human Plasma by Liquid Chromatography-Tandem Mass Spectrometry. Ther Drug Monit. 2018;40(4):417-24.
38. Tron C, Lemaitre F, Bros P, Goulvestre C, Franck B, Mouton N, et al. Quantification of infliximab and adalimumab in human plasma by a liquid chromatography tandem mass spectrometry kit and comparison with two ELISA methods. Bioanalysis. 2022;14(11):831-44.
39. Ordutowski H, Dal Dosso F, De Wispelaere W, Van Tricht C, Vermeire S, Geukens N, et al. Next generation point-of-care test for therapeutic drug monitoring of adalimumab in patients diagnosed with autoimmune diseases. Biosens Bioelectron. 2022;208:114189.
40. Kaur P, Chow V, Zhang N, Moxness M, Kaliyaperumal A, Markus R. A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. Ann Rheum Dis. 2017;76(3):526-33.
41. Velayudhan J, Chen YF, Rohrbach A, Pastula C, Maher G, Thomas H, et al. Demonstration of Functional Similarity of Proposed Biosimilar ABP 501 to Adalimumab. BioDrugs. 2016;30(4):339-51.
42. Bandyopadhyay S, Mahajan M, Mehta T, Singh AK, Gupta AK, Parikh A, et al. Physicochemical and functional characterization of a biosimilar adalimumab ZRC-3197. Biosimilars. 2014.
43. Huizinga TWJ, Torii Y, Muniz R. Adalimumab Biosimilars in the Treatment of Rheumatoid Arthritis: A Systematic Review of the Evidence for Biosimilarity. Rheumatol Ther. 2021;8(1):41-61.
44. Vande Casteele N, Gils A. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: Adding value to current practice. J Clin Pharmacol. 2015;55 Suppl 3:S39-50.
45. Balevic SJ, Rabinovich CE. Profile of adalimumab and its potential in the treatment of uveitis. Drug Des Devel Ther. 2016;10:2997-3003.
46. Nestorov I. Clinical pharmacokinetics of TNF antagonists: how do they differ? Semin Arthritis Rheum. 2005;34(5 Suppl1):12-8.
47. Ternant D, Karmiris K, Vermeire S, Desvignes C, Azzopardi N, Bejan-Angoulvant T, et al. Pharmacokinetics of adalimumab in Crohn's disease. Eur J Clin Pharmacol. 2015;71(9):1155-7.
48. Sharma S, Eckert D, Hyams JS, Mensing S, Thakkar RB, Robinson AM, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. Inflamm Bowel Dis. 2015;21(4):783-92.

Colophon

This guideline has been constituted by Auteurs: Dirk Jan A.R. Moes (PharmD, PhD, Clinical Pharmacologist), Nancy Loos (PharmD), E van Maarsseveen (PharmD, PhD, Clinical Pharmacologist) †, S.E. Berends (PharmD, PhD), Y Bijleveld (PharmD, PhD), Tessa Straatmeijer (MD PhD) under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)
Date: 21-12-2023

Appendices

Not applicable

Revision

-