Therapeutic Drug Monitoring

*IDK*monitor®

*IDK*monitor® Drug Level ELISAs

- for determination of drug level
- highly specific antibodies for drug binding

*IDK*monitor® ADA ELISAs

- for detection of anti-drug antibodies (ADA):
  free ADA ELISAs
  total ADA (drug tolerant) ELISAs

Also suitable for biosimilars and automatable!

immun diagnostik

www.immundiagnostik.com

*IDK*monitor®

Individual therapy monitoring through treatment with biologics

The treatment with biologicals is a very effective treatment option for patients suffering from a wide variety of different diseases e. g. inflammatory bowel disease or rheumatoid arthritis. Biological therapy gives patients a significant increase in life quality. However, while some patients do not respond at all to a treatment with a certain biologic (primary non-responder), others loose response in the course of the treatment (secondary non-responder), and thus they develop a resistance against the biologic. Furthermore, the treatment is very expensive and there are limited drugs available. This limited drug availability in combination with a potential drug resistance developing in the treated patient, shows the importance of **therapy optimisation** for a long-term therapeutic success.

Regular monitoring of the drug level, the formation of antibodies to the drug (ADA, anti-drug antibodies) and their concentration is important for a long-term therapeutic success, as it can detect and even prevent a secondary treatment failure at an early stage. At the same time, this allows an optimal patient-centred therapy and minimizes health care costs by avoiding unnecessary dose increases and therapies.

Both proactive and reactive monitoring are important. Regular monitoring (proactive monitoring) of the drug level and ADA measurements can be helpful in detecting and counteracting treatment failure at an early stage. Reactive monitoring in the event of acute treatment failure, however, allows informed decisions about how to proceed.

Drug Level ELISAs

The test systems for the quantitative determination of the active substance concentrations allow an assessment of the bioavailability of the selected biologic.

The effect of the biologics to a large extent depends on the serum concentration of the drug since bioavailability and pharmacokinetics are individual and vary during the course of disease. Monitoring of the drug level (especially the trough level) is therefore indicated to ensure that the drug is in sufficiently available in the circulation and, if necessary, to adjust its dose. In addition, a reduced trough level during the course of therapy indicates the existence of antibodies to the drug.

ADA ELISAs

The test systems for the detection of anti-drug antibodies (ADAs) provide information about the immune response to the respective biologics.

A therapy with biologics can lead to unwanted immune reactions if the patient produces antibodies to the drug. this could cause allergic reactions, decrease in efficacy as well as therapy failure can be the consequence. Although adjunctive therapy with immunosuppressants reduces the extent of ADA production, it is not always indicated. The monitoring of ADA levels allows an early intervention (e. g. increasing dose or frequency, addition administration of immunosuppressive drugs, switching to another drug) resulting in an individual, effective treatment with reduced side effects.

PANTS study

PANTS stands for "Personalising Anti-TNF Therapy in Crohn's Disease". Led by the University of Exeter and the Royal Devon & Exeter NHS Foundation Trust, this study is investigating primary and secondary treatment failure in patients with Crohn's disease treated with TNFα-blocking therapy throughout the UK.

Conclusion: Therapy failure of TNFα blockers is very common. Most of the times the cause is a too low trough level. The reasons for the low trough levels range from patient-individual pharmacokinetics to an immune response of the patient.

The results of the PANTS study suggest that TNFα-blocking therapies can be optimized by therapeutic drug monitoring (TDM). TDM can increase the effectiveness of the treatment.
In particular, PANTS data suggest that early personalized dosing controlled by trough level monitoring, combined together with the use of thiopurine or methotrexate therapy, may help achieve optimal drug levels and minimize the risk of antibody formation against the therapeutic antibody.

The PANTS study shows once again **how important personalized therapy is for patients with chronic inflammatory diseases** and **that *IDK*monitor® is a perfect tool for that purpose.**

Puclikation: N. Kennedy et al., "Predictors of anti-TNF treatment failure in anti-TNF-naïve patients with active luminal Chron's disease: a prospective, multicentre, cohort study", The LANCET Gastroenerology & Hepatology, Volume 4, Issue 5, P341-353, 2019

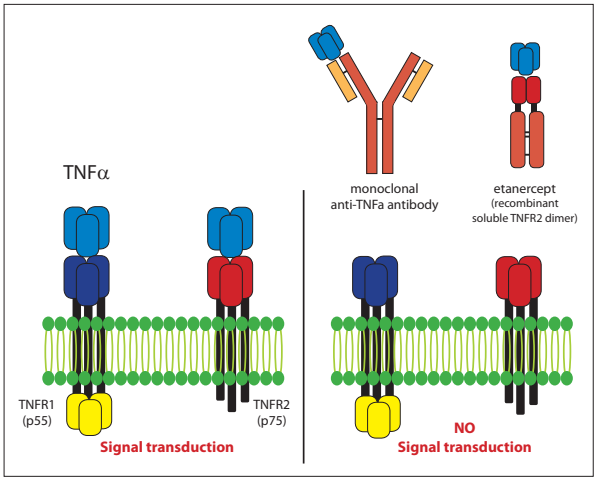
Additional literature:
- M.A.V. Willrich et al, „Lab Testing for Therapeutic Monocolonal Antibodies: A Retrospective Analysis for Adalimumab and Vedolizumab", EuroMedLab, 2019
- N.Plevris et al., „Higher Adalimumab Drug Levels during Maintenance Therapy for Crohn's Disease Are Associated with Biologic Remission", Inflammatory Bowel Disease, 2018

Mechanisms of action of the biologics belonging to the *IDK*monitor® product portfolio

TNFα

Tumor necrosis factor alpha (TNFα) is one of the pro-inflammatory cytokines that promotes and maintains inflammatory responses. The protein is produced by macrophages and T cells and plays a central role in both acute and chronic inflammation.
The TNFα concentration is greatly increased in many chronic inflammatory diseases (e. g. rheumatic diseases, Crohn's disease) and affects the development and clinical course of these diseases.
The overproduction of TNFα can be selectively inhibited by TNFα inhibitors (anti-TNFα antibodies).

Drugs:
infliximab
adalimumab
golimumab
etanercept
certolizumab

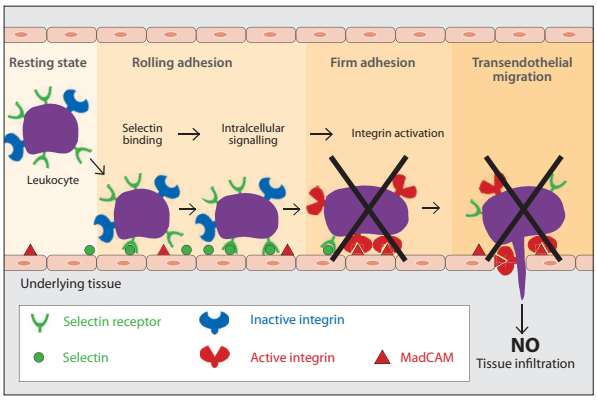


α4β7-integrin

The cell adhesion molecule α4β7-integrin is present on activated lymphocytes. Through binding to the MadCAM receptors, the α4β7 integrin allows lymphocytes to migrate into the intestinal mucosa. Thereby α4β7-integrin promotes and maintains inflammatory responses in the gut.

The binding of α4β7-integrin to the MadCAM receptors can be selectively inhibited by α4β7 integrin inhibitors. Since the presence of the MadCAM receptors is restricted to the gut, the effect of α4β7-integrin inhibitors is gut-specific.

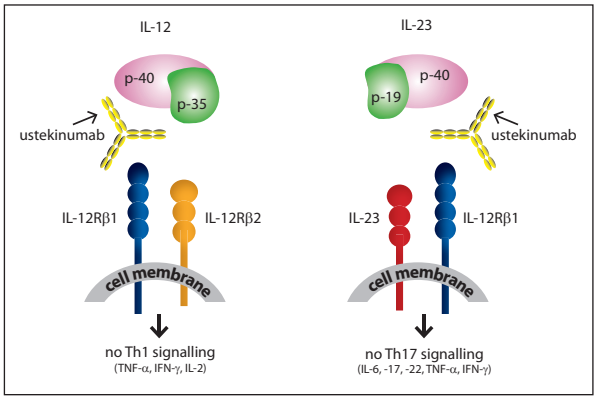
Drug: vedolizumab



IL-12/23

Interleukin 12 and 23 are cytokines that regulate the immune system and affect inflammatory responses that are stimulated by the immune system.
While IL-12 triggers the Th1 signalling cascade via receptors in the cell membrane, IL-23 is responsible for triggering the Th17 signalling cascade. Both lead to a maintenance of inflammatory reactions.
IL-12/23 inhibitors bind to the common subunit p40 of the two cytokines and thus prevent binding of the cytokines to the corresponding receptors. As a result, the inflammation-promoting signal cascade is prevented.

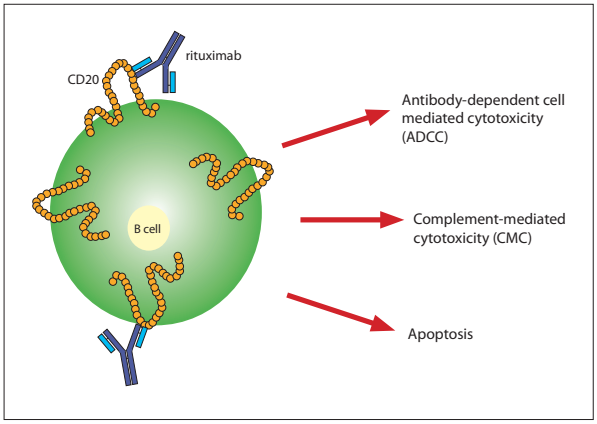
Drug: ustekinumab



CD20

CD20 (also: human B-lymphocyte-restricted differentiation antigen, Bp35) is a surface antigen on normal and malignant pre-B lymphocytes as well as on mature B lymphocytes. CD20 serves to optimise the B cell immune response, in particular against T cell-independent antigens, and may function as a calcium channel.
The CD20 antibody, through its binding to CD20, among other things, improves the action of natural killer cells (NK cells), which cause cell death in antibody-labelled B lymphocytes. This significantly reduces the number of living B lymphocytes, one of the goals of lymphoma therapy. In the treatment of autoimmune diseases, reducing the number of B lymphocytes also reduces the number of autoantibodies, leading to an improvement of the symptoms.

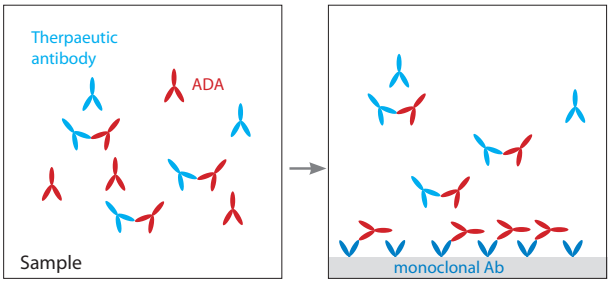
Drug: rituximab



Immundiagnostik offers two different test systems for the detection of ADA ELISAs:

*IDK*monitor® free ADA ELISAs

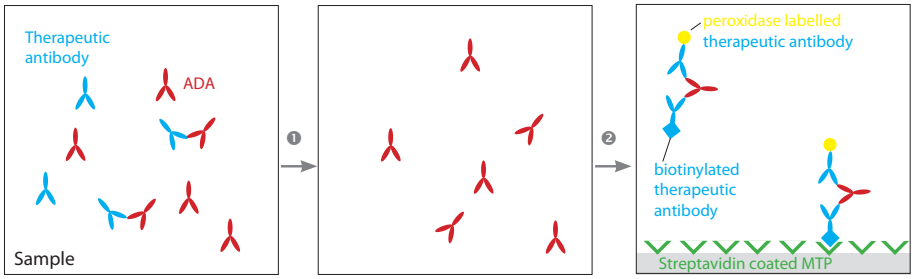
Free ADA are those that are not bound to the therapeutic antibody. On the one hand, this has technical consequences, namely that the free antibodies can only be determined if the drug level is low or undetectable. On the other hand, the presence of free ADA means that the patient's immune response produces more ADA molecules than circulating drug molecules are available.



No sample pretreatment necessary; free ADAs bind to the monoclonal antibody on the microtiter plate.

*IDK*monitor® total ADA ELISAs (drug tolerant assays)

The total ADA include the free and complexed antibodies. This means that even in the presence of a detectable drug level, the ADA concentration can be determined because the assays are drug tolerant. Thus, an early immune response can be detected, even if the drug level has not fallen off yet.



❶ Sample preparation: Dissociation of the therapeutic antibody from the drug-ADA complexes
❷ Complexation: Adding biotinylated and peroxidase labelled therapeutic antibody (conjugate + tracer).
Pretreated samples are added to the streptavidin coated microtiter plate; biotinylated therapeutic antibodies bind to streptavidin.

*IDK*monitor® product portfolio

Target	Drug	Drug Level Sample volume: 10 µL	Free ADA Sample volume: 25–50 µL	Total ADA Sample volume: 25 µL
TNFα	infliximab	✓ K 9655	✓ K 9650	✓ K 9654
	adalimumab	✓ K 9657	✓ K 9652	✓ K 9651
	golimumab	✓ K 9656	✓ K 9649	–
	etanercept	✓ K 9646	✓ K 9653	–
	certolizumab	✓ K 9662	–	–
α4β7-Integrin	vedolizumab	✓ K 9658	✓ K 9648	–
IL-12/23	ustekinumab	✓ K 9660	✓ K 9666	✓ K 9667
CD20	rituximab	✓ K 9661	soon available	–

- ***IDK*monitor® products for therapy monitoring products are the ideal combination for continuous monitoring of the course of therapy and medication management.**
- Products for TDM support well-informed decisions about stopping therapy, switching between biologics, or moving to a biosimilar.

With *IDK*monitor® products, you can measure both the original drugs as well as all biosimilars reliably and WHO-compliant!

US: all products: Research Use Only. Not for use in diagnostic procedures.

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